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SENILE PSYCHOSIS AND PELLAGRA*

A Report of Two Cases

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SEVERAL patients with psychoses of the senile type have been observed to improve after a period of therapy with niacin, thiamine, riboflavin and substances rich in the vitamin B complex. Review of their records has shown 2 with atypical pellagra. In view of the probable relation of pellagra to the clinically observed psychoses, these cases will be reported. The number of cases observed is not sufficient to warrant a statistical analysis, but the indications are that they are not infrequent.

* * *

The neuropsychiatric manifestations of pellagra in the early stages of the disorder are vague, consisting of irritability, weakness, lassitude, skeletal pains and severe malaise. As the disease advances more definite syndromes may appear — depressive states, manias, paranoid states, acute confusional states, agitated anxiety states and hallucinatory states. In the end stages, evidence of severe neurologic impairment may develop — stupor, convulsions, incontinence, impaired thermal regulation, muscular rigidity, irregular involuntary movements of the musculature, hypertonia, defective sensation and muscle paralysis. The manifestations may be solitary or occur in various combinations.[1–9]

Neurohistologic studies performed on pellagrins have revealed atypical neuronal and capillary changes distributed throughout the neuraxis,[10–13] especially in the cerebrum. Within the cortex the ganglion cells may lose their Nissl substance and eventually disappear. The extent of this change varies from case to case; as a rule it is most noticeable in the frontal lobes and in the hippocampus. In addition, there may be proliferation of glial tissue and of the endothelium of small vessels. In the subependymal regions the proliferative reaction may be the most noticeable.[10, 11] Circumscribed parenchymal changes are usually associated with such vascular lesions. These reactions are to be found in a wide variety of so-called "toxic" encephalopathies (central neuritis), as well as in pellagra.

Pellagrins with neuropsychiatric disorders have been treated successfully with niacin.[1–6] Some investigators have presented evidence that the results are more satisfactory when niacin is supplemented with other vitamins of the vitamin B group and a well balanced diet.[2, 5, 14]

The neuropsychiatric disorders that accompany old age may be considered in two categories — those arising primarily in the brain tissue and those secondary to an impaired circulation.

The first is an involution, a natural consequence of aging. It varies in intensity from a mild forgetfulness and a tendency to reminisce to extreme confusion, disorientation and dementia. The usual occurrence is in the years beyond the eighth decade, but similar conditions are known to affect persons in earlier life. When severe, the latter group may give rise to presenile dementias. These conditions are insidious and progress slowly.[15, 16] The pathologic alterations in the brains of patients so affected are notably a loss of neurons, neurofibrillary degeneration and the development of senile plaques or collections of amorphous deposit. Such changes are most noticeable in the frontal-lobe cortex, the Purkinje-cell layer of the cerebellum and the striatal portion of the basal ganglions.[17] Often there is a wide discrepancy between the severity of the clinical disorder and the extent of the pathologic change within the brain.[17, 18]

In the second type, the clinical disturbances are due to loss or impairment of parenchymal function as the result of impaired circulation. The syndromes produced may simulate those seen in the more advanced cases of the previous group, but oftener signs of focal lesions are present — hemiplegia, aphasia, agnosia and similar manifestations. The patients with vascular affection are more strikingly confused and disoriented than those in the other category; they have more vivid hallucinations. Lesions are likeliest to occur in the regions supplied by the middle cerebral artery and its branches. The size and extent of lesions vary from small

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ischemic foci involving the cortex alone to large infarctions affecting the whole hemisphere.

Although the differences between these two groups of patients may be recognized in some cases, Critchley[17] has stated, "We must admit that the distinction is more academic than practical, since in the great majority of cases the process of aging operates simultaneously on both the parenchyma and the blood vessels of the brain."

The occurrence of so-called "senile psychosis" in association with pellagra was noticed by Singer,[8] who concluded that in these cases pellagra is only incidental. Lorenz[9] observed a similar coincidence. He wrote:

> Chronic mental states largely ascribed to pellagra are those occurring late in life. A number of cases were observed showing typical senile dementia. These were all advanced in years and the occurrence of mental defects of this nature would have been expected. Likewise, a number of cases with marked peripheral arteriosclerosis showed a general mental enfeeblement such as is usually associated with sclerosis of the cerebral vessels. That these may have developed at a somewhat earlier period owing to the pellagra is not questioned. . . . These are probably instances in which pellagra served as a precipitating factor in the development of a psychosis of the senile or vascular type.

Rainsford,[19] Bonhoeffer,[20] Bigland[21] and McGregor[22] have reported cases that could have been similarly classified. Chittick and Stotz[23] quote Tompkins as stating that of 25 patients recovering from senile psychoses, 5 had had glossitis during the early stages of hospitalization, and this finding is believed by them to have been indicative of a nutritional deficiency state. Rothschild and Sharp[24] and Woltman[25] stress the importance of adequate nutrition in maintaining cerebral function in aged persons. Robinson[26] describes "toxic-delirious reactions of old age" and mentions the importance of metabolic and nutritional disturbances in precipitating such reactions. Wadsworth et al.[27] used vitamin B complex in the treatment of an unselected group of senile psychotic patients, with indifferent results. Palmer and his co-workers[28] reported on a group of 123 institutionalized senile psychotic patients; 30 of these recovered when given supportive therapy, which included large doses of vitamin preparations.

In neurohistologic studies of pellagra, Singer and Pollock[12] noted the occurrence of neurofibrillary ganglion-cell degeneration in some specimens, but made no mention of the ages of the patients from whom these were taken. Pearson[13] encountered a case with a clinical picture of a senile psychosis among a group of patients in whom central neuritis was found at autopsy. Although none of these findings are conclusive, they indicate the possibility of a closer relation between some of the senile psychotic episodes and pellagra.

Case Reports

Case 1. E. D., an emaciated 55-year-old woman, was admitted to the neuropsychiatric service of the University of Virginia Hospital on September 6, 1942. Her illness had begun late in 1929 with severe pains in the lower extremities. This was followed by progressively increasing weakness, which necessitated her remaining in bed. In addition, mental symptoms appeared, notably irritability, contrariness and emotional instability. Within several months after the onset the patient's appetite had failed and her food intake had decreased to half the usual quantity.

In the 9 succeeding years there were brief periods of partial remission, but otherwise the clinical picture remained unchanged despite medical care. In the summer of 1939 the patient became semistuporous and remained in that state for nearly a month. As a sequel to this, her intellectual function deteriorated further and her weakness increased. No further remissions occurred.

During the early part of 1942 the patient's emotional symptoms became exaggerated. On August 21, 1942, she lapsed into a stupor that persisted for 4 days. Recovery after this was very poor and the patient was hospitalized.

On admission the patient was confused, disoriented and agitated and complained of pains throughout the body. She was easily distracted, expressed paranoid and depressive ideas and prattled extensively. She had auditory and visual hallucinations of a morbidly violent character, which caused restless overactivity and often interfered with sleep. She echoed the gestures and speech of the examiner but was unable to perform skilled movements. She was moderately aphasic.

Physical examination revealed a dry skin. There were seborrheic excrescences in the nasolabial folds and macerations at the corners of the mouth. The oral and pharyngeal mucous membranes were dry and reddened. The tongue was magenta red. There were two shallow ulcers approximately 0.5 cm. in diameter on the posterior wall of the pharynx. The cardiovascular and respiratory systems were not unusual. The abdomen was normal. The musculature of the extremities was wasted and tender on deep pressure. The patient was unable to arise from bed because of generalized weakness. All the tendon reflexes were hyperactive, except at the left patella. Abdominal reflexes could not be elicited. The plantar reflexes were normal. Vibratory and position senses were severely impaired, producing a stereoanesthesia. Other neurologic findings were normal.

The red-cell count was 4,030,000, and the white-cell count 6600; the hemoglobin concentration was 12 gm. per 100 cc. The blood sugar concentration was 46 mg. per 100 cc., and the urea concentration 46 mg. Wassermann and Kahn reactions were negative. The urine was normal. Gastric analysis showed 12 units of free acid.

At the time of admission the patient refused to eat and had to be fed by gavage. Two days following admission treatment was instituted with large doses of nicotinic acid amide, riboflavin, brewers' yeast powder and thiamine chloride.* By the 6th day she was able to eat. The oral and nasolabial lesions cleared by the 7th day. The patient's mental acuity increased gradually and the bizarre patterns of thought disappeared, but the emotional lability persisted. In the early part of October treatment was supplemented with intramuscular doses of crude liver extract.† During the month intellectual function improved surprisingly‡ but the tongue remained magenta red, and the emotional reactions immature.

The patient was discharged on October 25. During the succeeding 2 months she remained well, but shortly after Christmas she again became irritable and lost her appetite. In late January, 1943, soreness of the tongue developed and the patient sought readmission.

At the second admission, the patient complained severely of gastrointestinal discomfort. Clinical, roentgen-ray and laboratory examinations revealed no organic lesion in the stomach or bowel. After treatment with crude liver extract and brewers' yeast powder there was gradual improvement, but vague neurotic complaints persisted. At no time did the magenta-red color of the tongue disappear. Treatment was continued after discharge, and no further recurrences were noted over a 10-month period.

*The daily dosages of vitamins were as follows: nicotinic acid amide, 0.6 to 1.05 gm. in divided doses by mouth; riboflavin, 0.01 to 0.02 gm. by mouth; thiamine chloride, 0.050 gm. parenterally; and brewers' yeast powder, 15.0 gm. by mouth.

†The daily dose of crude liver extract (Lederle No. 9083-291811), kindly supplied through the courtesy of Lederle Laboratories, Incorporated, Pearl River, New York, was 5 cc.

‡A full-scale Wechsler-Bellevue test on October 22 revealed an I.Q. of 125.

Comment. The duration of the disease in this case was unusual since one would not expect improvement of such degree after this length of time. The late manifestations were like those of a vascular disturbance, although the earlier ones were neurasthenic. The latter disturbances, the memory defects and the confabulatory episodes resembled the Korsakoff syndrome, which may occur in either the senile psychoses or in pellagra. The episodes of stupor were similar to those described in pellagrins by Cleckley and his co-workers.[3] The skin lesions were those of riboflavin deficiency, and the mucosal alterations were the combined effect of several deficiencies. The response to treatment puts this case definitely in the pellagra group.

Case 2. R. L. B., a 78-year-old man, was admitted to the medical service of the University of Virginia Hospital on October 31, 1942. Three days preceding admission he suffered a "stroke" and as a result became irrational.

Six years prior to admission he was hospitalized for an acute otitic infection. At that time he had choreiform tremors, but these were not described further. The blood pressure was then 150/85 and the urine had a specific gravity of 1.022 and was otherwise not remarkable. At a subsequent examination in 1938, no mention was made of any tremor. From 1939 to 1942 the patient had been under the care of his family physician for hypertension. During the last-mentioned year he had been having frequent slight "strokes" that resulted in progressive impairment of locomotion and in transient confusional states. The lower extremities "felt like blocks of wood" and he could not be sure of their position. On October 24, 1942, he suddenly became confused and lost the power of speech. He refused all food and fluid, developed a fever and within a few days became completely irrational.

At the time of admission the patient was noisy, inattentive and easily distracted. His emotional reactions were labile and he was overly concerned with religious matters. Motor and sensory aphasias, echolalia, echopraxia and perseveration of responses were present. The bladder and bowels were incontinent.

On physical examination, cachexia was noticeable. The skin was dry and thickened. The conjunctivas and scleras were hyperemic. The retinal vessels were slightly narrowed. The mucous membranes of the mouth and pharynx were reddened and edematous. A few carious teeth remained in the lower jaw; the peridental tissues were severely infected. The skin of the chest was covered with the lesions of a seborrheic dermatitis. The lungs were normal. The heart was clinically enlarged, and the rhythm was irregular owing to numerous extrasystoles. The blood pressure was 220/120. There were reducible bilateral inguinal hernias. A shallow decubitus ulcer overlay the sacrum. There was extensive peripheral arteriosclerosis. There were uncontrolled irregular movements of the extremities. The musculature was weak and wasted. All the tendon reflexes were hyperactive, especially on the right side. The abdominal reflexes were easily fatigued. The right plantar reflex was extensor and the left one normal. The special senses could not be evaluated, but otherwise the functions of the cranial nerves appeared normal. General sensibility was such that only strong thermal and painful stimuli evoked any responses. Sucking reflexes could be elicited, and a grasping response was present in the right hand.

The red-cell count was 5,300,000 and the white-cell count 12,000. There was a hemoglobin concentration of 16.5 gm. per 100 cc., and a blood urea concentration of 86 mg. The Wassermann reaction was negative. The plasma carbon dioxide combining power was 58.6 vol. per cent. The urine contained a small amount of albumin, and an occasional leukocyte was seen in each high-power field of the sediment. The cerebrospinal fluid was normal.

Several hours after admission, treatment was started with infusions of physiologic saline solution containing 5 per cent of glucose. On the following morning the red-cell count was 4,700,000, the hemoglobin concentration 13 gm. per 100 cc. and the urea concentration 53 mg. The urine did not contain measurable amounts of albumin. Infusions were administered over the next few days, without change in the neuropsychiatric picture, and the patient was transferred to the closed ward.

On the 5th day, the treatment was modified to include large doses of nicotinic acid amide, thiamine chloride, riboflavin and brewers' yeast powder.* Within 3 days the disturbances of speech and behavior cleared and the patient became tidy and co-operative. By the 15th day all neurologic signs had returned to normal and the parenteral vitamin and saline therapy was discontinued. The patient's condition continued to improve steadily, his memory returned except for the period of his confusion, and he stated that he felt as though he had had a bad dream. He was discharged on the 23rd day, and remained well for the succeeding 9 months.

In the latter part of August, 1943, the patient became quite stubborn. Periodically thereafter he was confused, ordered his wife and daughter from the house, and on one such occasion attempted to beat them. By October he refused all nourishment except an occasional teaspoonful of milk.

On October 10 the patient suffered a series of convulsive seizures, and on October 12 he was readmitted to the neuropsychiatric ward. Examination at that time revealed severe dehydration. There were pellagrous skin changes on the hands and other exposed parts. The mucous membranes of the mouth and pharynx were reddened, and there was a small ulcer in the pharynx. The conjunctivas were injected. The cardiac status was not different from that of the previous admission. The blood pressure was 215/115. The patient was dysarthric, disoriented as to time and place, restless, inattentive and confused. No significant changes were noted in the eye grounds. The tendon reflexes were normal. The abdominal reflexes could not be elicited, and the plantar responses were flexor. Hoffmann's sign was positive in the left hand. Sensory examination demonstrated much the same phenomena as those elicited on the preceding admission. Co-ordination was so poor that the patient was unable to stand, even with assistance. Laboratory studies revealed no significant deviations from the normal.

On the day following admission administration of large doses of the crystalline vitamins was started. Within a week, all the oral and skin lesions had healed. The patient's emotional reactions improved and he regained the use of his extremities in locomotion. During the hospital stay the blood pressure fluctuated widely but usually remained below 150/90. The patient was discharged 11 days following admission, at which time there were no clinical signs of the neuropsychiatric disturbance. Re-examination over a 4-month period indicated continued minor emotional instability, although the patient was receiving maintenance doses of nicotinic acid amide.

Comment. This case illustrates the effect of nutritional inadequacy in a patient with a subclinical encephalopathy of the combined senile-vascular type. The re-establishment of adequate neurologic function and the concurrent disappearance of the somatic signs of deficiency under quasi-controlled therapy indicate that the neuropsychiatric dysfunction was related to the biochemical imbalance. The status of the patient between exacerbations suggests that the clinical picture in the acute phases was largely determined by the underlying aging processes within the brain.

Discussion

The neuropsychiatric manifestations of pellagra usually appear after dermal, oral or gastrointestinal manifestations have developed. In a small proportion of cases, however, neuropsychiatric signs alone are manifest. Elvejhem[14] in reviewing the relation between nicotinic acid and pellagra observed that central nervous tissue retained its ability to oxidize glucose even with severe diminution of the concentration of co-zymase in the tissue fluids. Such a finding indicates that other factors may play an important role in altering the so-called "resistance" of nervous tissue to nicotinic acid deficiency.

*The daily dosages of vitamins were as follows: nicotinic acid amide, 0.1 gm. intravenously; riboflavin, 0.01 gm.; thiamine chloride, 0.05 gm. intravenously; and brewers' yeast powder, 15.0 gm.

The major neurohistologic changes in the senile psychoses and in pellagra overlap somewhat in the frontal lobes and in the deeper ganglions. A combination of these two pathologic processes may result in clinical disturbances when either alone is of insufficient magnitude to produce symptoms. Under these conditions a clinical neuropsychiatric disorder may be present with but minimal extraneural signs of pellagra.

The senile person is apt to become mentally disturbed during the course of acute febrile illness, following severe trauma and under emotionally unfavorable conditions. As yet, this liability has not been fully explained. This type of occurrence is evidence of the increased susceptibility of the aging nervous system to adverse environmental changes. Such susceptibility may be attributable to the organic changes within the nervous systems of such patients, just as are the personality changes of the aged.

Personality changes also become manifest in the dietary. Restrictions, both qualitative and quantitative, are not infrequent among elderly patients. Fadism of this sort tends to eliminate valuable foodstuffs from the diet, and its continuation may lead to clinical deficiency states. In this way a cycle is formed in which a fad leads to an inadequate food intake, and the inadequacy to a further loss of appetite and a severer dietary restriction.

The diagnosis of pellagrous encephalopathy in the aged person with psychosis must depend on clinical or laboratory evidence of nicotinic acid deficiency. The neuropsychiatric syndromes produced are not characteristic of pellagra but of the location of the lesions in the central nervous system, and they may occur in a variety of disorders. The response to controlled therapy may be of value in this regard, in which case the diagnosis may be made in retrospect. In general, mucosal and dermal lesions of nicotinic acid or riboflavin deficiency should be sought whenever an aged psychotic patient is examined. Evidence of other nutritional disorders should lead one to investigate further.

Treatment should be largely prophylactic. Persons in the late decades of life should have diets of optimal rather than minimal adequacy. When the maintenance of an adequate diet becomes infeasible, dietary supplements should be administered. For this purpose either the crystalline vitamins or concentrated extracts may be used. Crystalline preparations may be given parenterally to patients whose intestinal absorption is defective. When deficiency already exists, effective treatment should combine the above modes of administration. Adequate returns may be expected from adequate nutrition, even in the aged.

Summary

Senile psychosis may be simulated by pellagrous encephalopathy in the aged. The underlying neurologic alterations in the elderly patient may predispose to this occurrence.

The senile-pellagrous type of encephalopathy may respond well to treatment with crystalline vitamin B products or with natural vitamin B concentrates. The recognition of this group of cases may permit effective therapy.

The maintenance of an optimal dietary by the normal aged person as well as by the senile invalid should be a matter of primary importance.

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ACUTE INFECTIOUS LYMPHOCYTOSIS IN YOUNG ADULTS

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ACUTE infectious lymphocytosis, a clinical entity featured by a benign relative and absolute increase in the number of small mature lymphocytes, was first described in 1941 by Smith.[1] He presented 2 cases of this disease and expressed the opinion that the group of patients reported by Reyersbach and Lenert[2] and 1 case described by Wilson and Cunningham[3] belonged in this classification rather than among the cases of infectious mononucleosis, as reported. There were no significant clinical signs or symptoms in any of these cases. Another case of acute infectious lymphocytosis presenting a marked symptomatology has been described,[4] and the belief was expressed that 2 of the cases reported by Thelander and Shaw[5] as infectious mononucleosis should be classified as acute infectious lymphocytosis. Smith[6] has recently summarized his experience with acute infectious lymphocytosis and has described 4 additional cases.

To date, all reported cases of acute infectious lymphocytosis have occurred in children under the age of nine. It seemed of interest, therefore, to present 2 cases in young adults.

CASE 1. A 20-year-old soldier was admitted to the station hospital on August 25, 1943. Rubeola and epidemic parotitis had occurred in childhood. Otherwise, the past history was not significant. The family history was noncontributory.

For 1 week prior to admission, the patient had a "cold," accompanied by intermittent pains in the back and chest. Additional complaints of stomach cramps, headache and a mild, nonproductive cough eventually developed; fever was demonstrable and the patient was hospitalized.

The temperature on admission was 102°F. Physical examination revealed a slender, well developed young adult appearing neither acutely nor chronically ill. The throat was mildly inflamed, and there was a small collection of mucus in the posterior pharynx. A small, tender lymph node was palpable in the right submaxillary region. The remainder of the examination was normal.

The symptoms completely disappeared within a few hours after admission, but during the first 2 weeks of hospitalization the temperature was elevated each morning to from 99 to 101°F., dropping to normal each afternoon or early evening. On August 30 there appeared a generalized morbilliform rash, which gradually faded and disappeared 4 days after onset. With its disappearance, a few small, nontender, axillary and inguinal lymph nodes became palpable. One week later, these were no longer felt. On September 13, the afternoon temperature was 100.2° F., rising to 104° F. the following day. There was then a rapid fall in the temperature, but the patient continued to run a low-grade fever every morning until discharged on September 27.

Agglutination reactions for *Eberthella typhosa*, *Salmonella paratyphi*, *Salmonella schottmülleri* and *Brucella abortus* and the Weil–Felix reaction were negative. A roentgenogram of the chest showed no abnormalities. Repeated examination of the urine gave results within normal limits. The Kahn reaction was negative. The electrocardiograph recorded normal tracings. Heterophil agglutination tests on September 3 and 13 gave negative reactions.

There was a moderate relative and absolute increase in the number of lymphocytes of approximately 2 weeks' duration (Table 1). Its onset occurred during the 1st week, the white-cell count, which had been normal on admission, increasing to 27,850 by the 7th day. Frequent examination of stained smears failed to reveal abnormal or atypical lymphocytes. Small mature lymphocytes accounted for the lymphocytosis. The proportion of large mononuclear cells never exceeded 5 per cent. Repeated determinations of the erythrocyte and total polymorphonuclear-cell counts and hemoglobin content were within normal limits. Platelets were always present in the smear in adequate numbers.

TABLE 1. *White-Cell and Lymphocyte Counts in Case 1.*

DATE	WHITE-CELL COUNT	LYMPHOCYTES			
		SMALL	LARGE	TOTAL	LYMPHOCYTE COUNT
		%	%	%	
8/26	6,400				
9/2	28,000	83	1	84	24,000
9/3	20,000	77	5	82	16,000
9/4	14,000	76	0	76	11,000
9/5	18,000	60	5	65	12,000
9/6	19,000	77	4	81	15,000
9/8	13,050	77	0	77	10,000
9/11	10,000	57	2	59	5,900
9/15	12,000	46	2	48	5,800
9/21	8,700	37	4	41	3,600

CASE 2. A 19-year-old soldier was hospitalized on January 25, 1944. The family and past histories were noncontributory. The patient recalled epidemic parotitis, pertussis and varicella during childhood.

During the day preceding admission, the patient had noted a slight fever, a mild nonproductive cough, frontal headache and nasal obstruction. He was well developed and well nourished. A slight hyperemia of the conjunctivas, nasal mucosa and pharynx was the only abnormal finding observed on physical examination. The temperature on admission was 99.4° F., but thereafter was normal. The patient became asymptomatic 24 hours following hospitalization. Signs of the mild upper respiratory infection persisted for 4 days. Lymph nodes of significant size were never palpable.

A culture of the throat yielded *Staphylococcus albus* and a few pneumococci. A roentgenogram of the chest revealed no abnormalities. Urinalysis gave results within normal limits. The Kahn reaction was negative. Examination of the spinal fluid on January 28 was negative except for a cell count of 40, 40 per cent of which were lymphocytes and 60 per cent polymorphonuclear leukocytes. Re-examination of the spinal fluid on February 5 showed that the cells had dropped to 2 polymorphonuclear leukocytes per cubic millimeter. Heterophil agglutination tests on January 28 and February 5 and 15 gave negative reactions.

A moderate lymphocytosis caused by small mature lymphocytes was likewise present in this patient (Table 2); it was observed over a period of 2 weeks. The maximum white-cell count was 22,000. No immature or atypical lymphocytes were seen at any time. The proportion of large mononuclear cells did not exceed 6 per cent. The platelet count varied

TABLE 2. *White-Cell and Lymphocyte Counts in Case 2.*

DATE	WHITE-CELL COUNT	LYMPHOCYTES			
		SMALL	LARGE	TOTAL	LYMPHOCYTE COUNT
		%	%	%	
1/25	22,000	65	2	67	15,000
1/26	15,000	63	5	68	10,000
1/27	20,000	65	5	70	14,000
1/28	22,000	55	5	60	13,000
1/29	16,000	64	2	66	11,000
1/30	12,000	62	3	65	7,800
1/31	13,000	68	5	73	9,500
2/1	14,000	57	5	62	8,700
2/2	15,000	58	5	63	9,500
2/3	9,300	38	6	44	4,100
2/4	11,000	40	5	45	5,000
2/5	8,300	37	4	41	3,400
2/6	14,000	31	5	36	5,000
2/9	8,800	31	4	35	3,100
2/15	9,000	25	5	30	2,700
2/19	7,500	23	6	29	2,200

from 225,000 to 315,000. Repeated determinations of the hemoglobin content and the number of red cells were normal. The total number of polymorphonuclear leukocytes was constantly within the normal range. The bleeding and clotting times of the blood were normal.

Discussion

The evidence for the establishment of acute infectious lymphocytosis as a specific entity has recently been summarized by Smith.[6] He differentiates it from infectious mononucleosis, acute lymphatic leukemia and other infections associated with a lymphocytosis in children. The reader is referred to his paper for a comprehensive discussion.

I have encountered one other, apparently rare, consideration in the differential diagnosis of an absolute lymphocytosis in children. A relative and absolute increase in the number of small mature lymphocytes was observed during the administration of sulfadiazine to a child with a purulent otitis media in whom the initial reaction of the blood was that of a polynucleosis. The extent of the lymphocytosis was similar to that experienced in acute infectious lymphocytosis in children, but the white-cell count promptly returned to normal following discontinuance of the drug.

Study of the present 2 cases of acute infectious lymphocytosis in adults indicates that the disease is closely similar to that observed in children. Both patients had clinical evidence of a mild upper-respiratory infection. In addition, Case 1 presented symptoms usually attributed to a mild infection of the influenzal type. Both had clinical courses similar to that noted in several of the children previously reported (Cases R. S. and E. S.[6]). The patient in Case 1 had a morbilliform rash lasting for four days during the first week of the disease. A rash of this type has not been previously encountered in acute infectious lymphocytosis. It was similar to the rash reported in 5[7] to 18.5[8] per cent of cases of infectious mononucleosis. An extremely irregular febrile reaction was observed in Case 1 throughout most of the period of hospitalization. Similar temperature curves were observed in 2 of the children with acute infectious lymphocytosis (Case E. N.[4] and Case M. S.[6]).

As stated above, the spinal fluid early in the course of the disease in Case 2 contained 40 cells per cubic millimeter, only 40 per cent of which were lymphocytes. This finding was similar to that encountered in 2 children reported by Thelander and Shaw.[5] Although these patients presented symptoms of meningitis and encephalitis, respectively, there were no signs or symptoms, except for headache, referable to the nervous system in Case 2. The spinal fluid has been examined in only 1 other case of this disease (Case M. S.[6]) and was found to be normal. One other child with acute infectious lymphocytosis presented symptoms compatible with neurologic involvement, but examination of the spinal fluid was not done.[4] Smith[9] has recently encountered 2 children with acute infectious lymphocytosis in whom the clinical picture resembled that of poliomyelitis. Collectively, these cases indicate neurologic involvement in an appreciable percentage of reported cases of acute infectious lymphocytosis, and suggest that this disease be included in the differential diagnosis of patients presenting neurologic signs and symptoms in association with an acute febrile illness.

The duration of the absolute lymphocytosis in adults appears to be shorter than that observed in children. The latter usually have elevated lymphocyte counts for periods of three to five weeks, in contrast to the shorter intervals observed in the present adult cases. Likewise, the maximum leukocyte counts of 27,850 and 22,000 encountered in the present cases were well below the usual range of 40,000 to 110,000 in children. A leukocytosis of 18,600 encountered in an eight-year-old girl has been the only exception to this range in children (Case E. S.[6]). All other aspects of the hematologic picture in the present cases were similar to those previously described.

Infectious mononucleosis presents the greatest problem in the differential diagnosis of acute infectious lymphocytosis in adults. Although still to be considered, the other diseases discussed in the differential diagnosis of acute infectious lymphocytosis by Smith[6] are not so frequently encountered in adults. From August 1, 1943, to August 1, 1944, 12 cases of a relative and absolute lymphocytosis were observed in this station hospital. The cases of acute infectious lymphocytosis were the only ones encountered up to February 5, 1944. Ten cases of infectious mononucleosis were observed during the following five-month period. Although histories were obtained of contact between several of the patients with infectious mononucleosis, there was no possible contact between the patients with the two diseases. In spite of certain similarities, careful clinical, hematologic and serologic study of these cases corroborated the factors of differentiation between infectious mononucleosis and acute infectious lymphocytosis stressed by Smith.[6]

Clinically, the patients with infectious mononucleosis were sicker and for a longer period than those described in detail in this paper. The symptomatology of the cases of infectious mononucleosis conformed to that described in recent reviews.[7, 10] In most of the reported cases of acute infectious lymphocytosis, the clinical findings have been minimal or completely absent. It must be remembered, however, that there have been cases (Case E. N.[4] and Case M. S.[6]) in which the clinical picture was that of an acute and severe illness. The 10 cases of infectious mononucleosis had a marked lymphadenopathy, which sharply demarcated them from the minimal amount or complete absence of lymph-node enlargement encountered in the 2 cases of acute infectious lymphocytosis.

The principal point in the differential diagnosis of these diseases was made by frequent examinations of the peripheral blood smear throughout the course. The maximum white-cell counts in both diseases fell within the same range. Thus, the extent of the count in adults cannot be used as a point of difference between the two diseases as it is in children, in whom the leukocytosis in acute infectious lymphocytosis is much higher than it is in infectious mononucleosis. Although there was considerable variation in the number of large atypical mononuclear cells in the differential smear from day to day in the cases of infectious mononucleosis, they were always present in significant proportions (8 per cent or more). Repeated examinations of the peripheral blood smear in the cases of acute infectious lymphocytosis failed to reveal the presence of these large atypical mononuclear cells at any time. The lymphocytosis was due in its entirety to small, mature lymphocytes. Although not sharply differentiated, the period of absolute lymphocytosis in the cases of infectious mononucleosis tended to be shorter — five to twelve days — than that encountered in the cases of acute infectious lymphocytosis, although it is well known that in the former the lymphocytosis may continue for months. Most of the cases of infectious mononucleosis showed a rather persistent relative lymphocytosis, with the continued presence of large atypical mononuclear cells, whereas the cases of acute infectious lymphocytosis returned promptly to a normal differential once the period of the absolute lymphocytosis had been completed.

The heterophil agglutination reaction has been uniformly negative in all cases of acute infectious lymphocytosis. In a recently reported series of 143 cases of infectious mononucleosis, the reaction was positive in significant titers (1:64 or higher) in 83 per cent.[7] Nine of the 10 patients with infectious mononucleosis in the present study had titers of 1:64 or higher. The remaining patient, who presented typical hematologic findings, had a maximum titer of 1:28. Therefore, the heterophil agglutination reaction appears to be a negative laboratory test of considerable importance in the differential diagnosis of acute infectious lymphocytosis.

A review of the present literature on acute infectious lymphocytosis suggests that this disease is infrequently encountered. It is obvious that, with the minimal and varied clinical findings of many of the reported cases, the diagnosis of this disease will be missed unless a hematologic study is routinely accomplished. On the other hand, a more widespread familiarity with the varied manifestations of acute infectious lymphocytosis will result in its detection in a frequency greater than the reported cases indicate.

Summary

Two cases of acute infectious lymphocytosis occurring in young adults are reported. The hematologic findings were similar to those previously recorded in children except that the extent of the lymphocytosis was less and its duration was shorter. A morbilliform rash was present for four days in Case 1, a finding not previously described in this disease. Changes in the spinal fluid were observed in Case 2, without clinical evidence of involvement of the nervous system.

The clinical, hematologic and serologic findings in these cases are compared with those in 10 cases of infectious mononucleosis.

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CLINICAL NOTE

PEDICULOSIS CORPORIS AND LEG ULCERS*

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WHEN a middle-aged patient confronts a physician with ulcers of the legs for diagnosis and treatment, immediately such causes as venous

FIGURE 1.

stasis, late spirochetal infection, cancer, erythema induratum, tuberculosis, sickle-cell disease, ecthyma, trauma, diabetes and self-infliction are considered. The dermatologist if consulted thinks also of deep mycologic infection, — blastomycosis, sporotrichosis, actinomycosis and so forth, — phagedenic ulcers, microaerophilic hemolytic streptococcus infections, drug (especially halogen) ingestion, leprosy, mycosis fungoides, necrobiosis lipoidica diabeticorum, scleroderma, leishmaniasis, cutaneous diphtheria, flea bites and tropical ulcers. To this list should be added the bites of the body louse, with the resultant scratching, infection and ulceration. In a large hospital clinic, ulcers of the legs due to pediculosis corporis rank second in frequency only to the so-called "stasis" (varicose) ulcers.

Several excellent textbooks on dermatology[1-4] fail to mention such ulcerations in the discussion of either pediculosis or ulcers. Other textbooks[5, 6] mention that ulcerations may occur but fail to stress adequately their occurrence on the legs. Thus, it is good practice to examine the entire body and clothing of patients with unexplained ulcers of the legs.

The ulcers are usually bilateral and multiple, and are most numerous on the lower third of the leg (Fig. 1). They are shallow, oval or rounded (but may occasionally have straight sides), and generally ooze a syruplike fluid. They are ordinarily surrounded by an area of erythema. The legs frequently show localized hemorrhagic scratch marks, but the typical parallel linear scratch marks of pediculosis corporis are not usually present.

Such lesions respond well to eradication of the body lice, followed by the local application on alternate days of a 1 per cent aqueous solution of gentian violet and 2 per cent allantoin in a water-soluble emulsion base.

SUMMARY

Multiple ulcers of the legs are frequently due to infestation of the clothing with body lice. Search for such parasites should be made in all suspicious cases.

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MEDICAL PROGRESS

MYCOTIC INFECTIONS (Concluded)*

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SYSTEMIC MYCOSES

Included in this category are diseases caused by a wide variety of fungi, each of which may invade any tissue of the body, producing widespread infection resulting in death. These fungi induce a granulomatous type of infection, and differential diagnosis must include tuberculosis, syphilis, granulomas and neoplasms.

Coccidioidomycosis

This is a highly infectious disease caused by *Coccidioides immitis* that produces a high incidence of infection, as shown by positive skin tests with coccidioidin, among native populations in the endemic areas of the San Joaquin Valley in California, around Phoenix and Tucson in Arizona and around San Angelo in central western Texas. Scattered cases have been reported from other areas in the United States, but most of them can be traced back to the localities mentioned above. A few cases have been reported from outside the United States, namely, South America, the Hawaiian Islands and Italy.

The fungus appears in the sputum, exudates and tissues as a large, single-celled, thick-walled spherule that reproduces by endosporulation. In culture, the fungus grows as a filamentous mold and reproduces by means of arthrospores, spores produced by fragmentation of its filaments.

Coccidioidomycosis is recognized as a pulmonary infection contracted by inhalation of the arthrospores of the fungus in dust; it simulates tuberculosis in all its clinical manifestations. The disease is divided into an acute primary infection of the lungs, usually followed by complete recovery, and a chronic progressive secondary granulomatous infection with a mortality rate of approximately 50 per cent.

The acute primary infection, with an incubation period of eight to fourteen days, simulates a cold, "flu" or bronchopneumonia. The symptoms may be mild or range in severity to severe prostration with chills, fever, malaise, anorexia, night sweats, headache, backache, pleurisy and rapid loss of weight. Physical signs in the chest are usually absent, and the x-ray films may be clear or may be indistinguishable from those of primary tuberculosis. Such an x-ray picture of the lungs clears rapidly, however. In about 2 to 5 per cent of such infections an associated hypersensitivity develops in five to fourteen days, manifested by erythema nodosum or erythema multiforme. Such skin lesions vary in duration from one to eight weeks, but the pigmentation may remain for months. Diagnosis is established by finding the large, nonbudding, endospore-filled spherules in the sputum, by culture and animal inoculation and by a skin test with 0.1 cc. of a 1:1000 dilution of coccidioidin. Complement fixation and precipitin tests, using coccidioidin as the antigen, are useful diagnostic acids.

The chronic secondary progressive granulomatous infection is the result of an endogenous dissemination of the fungus either during the initial infection or later. Any organ of the body may be infected, and the symptoms are indistinguishable from those of tuberculosis. Demonstrating the organism is the only satisfactory means of establishing the diagnosis. Serologic (complement fixation and precipitation) tests are usually positive, but owing to the severity of the disease the patient may be anergic and give a negative skin test even with a 1:10 dilution of coccidioidin.

Treatment of the primary infection is symptomatic. Salicylates are helpful, but there is no specific treatment. Bed rest until the sedimentation rate and white-cell count are normal and until the lung findings, if any, show progressive clearing is all that can be accomplished. Recovery without sequelae should be expected.

Treatment of the secondary progressive infection is not satisfactory, and the mortality rate approaches 50 per cent. Many drugs have been used, but no consistent method of treatment has been established. Bed rest with a high-vitamin, high-calorie diet, as with tuberculosis, is advocated to support any resistance to the infection that the patient may have.

From 1894 to 1896, when Rixford[80] and Rixford and Gilchrist[81] first described this infection in the United States, until 1936, the disease was known as coccidioidal granuloma and thought to be highly fatal. Gifford[82] and Dickson,[83–86] however, established the fact that a disease known locally in the San Joaquin Valley as "valley fever," "San Joaquin Valley fever," "desert fever" or "desert rheumatism" was a benign nonfatal form of coccidioidal granuloma not previously recognized.

Epidemiologic studies of this disease have shown that the fungus occurs in the soil,[87–89] in wild ro-

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dents,[90, 91] cattle and sheep[92–97] and in dogs that have lived in endemic areas.[98] The disease is acquired by inhalation of windblown dust laden with the spores of the saprophytic cultural form of *C. immitis* and not by a person to person or an animal to person transfer of the spherules found in the human or animal tissues during the disease.[99]

North American Blastomycosis

North American blastomycosis or Gilchrist's disease is a chronic infection caused by *Blastomyces dermatitidis*, with characteristic skin lesions and systemic involvement, particularly of the lungs, that is indistinguishable clinically from tuberculosis. The disease seems to be confined to the United States and Canada, since no adequately proved cases have been reported elsewhere.

B. dermatitidis appears in the sputum, exudates and tissues as a large, round, thick-walled, single budding organism. Cultured at incubator temperature, the fungus remains in the budding yeastlike parasitic form. Cultured at room temperature, however, the fungus develops a filamentous growth that reproduces by conidial formation from the sides of the filaments or from the ends of short branches.

In cutaneous blastomycosis the lesions occur on the exposed parts of the body, — face, neck, dorsum of hands, wrists and forearms, ankles and forelegs, — where they resemble the lesions of verrucous tuberculosis cutis or epitheliomas. Beginning as a papulopustule, such lesions slowly spread peripherally, break down to reveal a red granulating base covered with a dirty pink exudate and a raised papilliform or verrucous border with miliary-like abscesses. Occasional lesions seen in the genitorectal region should not be mistaken for granuloma inguinale. The clinical diagnosis is confirmed by demonstrating the large, round, thick-walled, single budding fungus in the exudate, crusts or pus from the peripheral miliary abscesses.

Systemic blastomycosis closely mimics tuberculosis. The fungus enters the body by way of the respiratory tract, and the lungs, skin and bones are the most frequently involved organs. Multiple subcutaneous gummalike nodules may appear anywhere on the body, and rupture to free a bloody pus. With widespread blood-stream dissemination of the fungus, the liver, spleen, kidneys and central nervous system are the usual sites of infection. The spleen and liver lesions are minimal, and the intestine is not invaded. Until skin involvement by subcutaneous abscess formation occurs, tuberculosis is the usual diagnosis. All attempts should be made, however, to find the fungus in the sputum or exudates when repeated examinations for the acid-fast tubercle bacillus are negative.

Treatment should not be started on any case of blastomycosis until an intracutaneous skin test with 0.1 cc. of heat-killed vaccine of the fungus has been done to determine the sensitivity of the patient to the fungus or its products. Martin and Smith[100] have shown that lesions of patients sensitive to such materials rapidly spread when iodides or x-rays, or both, are used. Patients found not to be sensitive may be started immediately on potassium iodide by mouth or sodium iodide intravenously, whereas those patients who are sensitive should be given a course of desensitization before iodides are administered. Good results in the treatment of cutaneous blastomycosis should be expected. Results of the treatment of systemic blastomycosis depend on an early diagnosis and the immunologic status of the patient, as outlined by Conant et al.[101]

Since blastomycosis was described by Gilchrist[102] in 1896 and the fungus named *B. dermatitidis* by Gilchrist and Stokes[103] in 1898, several different fungi have been isolated from the disease and described as new genera or species. Comparative studies of these different fungi by Benham[104] and Conant[105] have shown them to be identical and the disease to be caused by a single etiologic agent.

The source of infection with *B. dermatitidis* has not been proved. Stober[106] isolated a white mold from the dwelling of a patient, but the fungus was not sufficiently described to prove it to be *B. dermatitidis*. Because of this report, it was thought that poor, unhygienic living conditions allowed contact with the fungus, which could be found in such places. There is evidence, also, that the fungus occurs in nature and that cutaneous blastomycosis is contracted by an introduction of the organism into the skin through abrasions or trauma. Toepel[107] reported a case following a thorn prick, and McKenty and Morgan[108] one from a scratch on the face; Robinson[109] described a patient whose onset followed a barefoot walk.

Ravogli,[110] Werley[111] and Wohl[112] suggested the possibility that the disease was contracted from handling animals or their products, but failed to show the fungus in such materials. That animals do have the disease has been shown by Martin and Smith[113] and Foshay and Madden[114] in their reports of spontaneous infections in dogs. There has been, however, no proved transmission of the fungus from animal to man. The single transmission from man to man was reported by Evans[115] in a physician who, at necropsy of a case of blastomycosis, cut his finger.

There seems to be no endemic area of the disease. Sporadic cases occur throughout the United States, and the lack or number of cases is an index only of the interest shown in the disease.

South American Blastomycosis

South American blastomycosis, paracoccidioidal granuloma or Lutz–Splendore's disease is a chronic granulomatous disease of the mucous membranes of the mouth and regional lymph nodes, skin of the face and internal organs caused by *Paracoccidioides brasiliensis* or *P. cerebriformis*. The disease is largely confined to Brazil, but is reported occasionally from

other countries in South America, namely, Argentina, Paraguay, Peru and Venezuela.

P. brasiliensis and *P. cerebriformis* appear in the pus, exudates or scrapings from the lesions as large, round, multiple budding, thick-walled organisms. The buds, arranged around the periphery of the parent cells, may be as small as cocci (1 to 2 microns) or 30 microns in diameter. Cultured at incubator temperature these fungi develop yeastlike colonies not unlike those of *Blastomyces dermatitidis*. The multiple budding, parasitic tissue forms are found in such cultures. When cultured at room temperature, *P. brasiliensis* develops a filamentous colony that is cottony and *P. cerebriformis* develops a filamentous colony that is waxy, being smooth or wrinkled.

This disease has been divided into three distinct types — the mucocutaneous, the lymphangitic and the visceral. In the mucocutaneous type of infection, the portal of entry is the mouth, with ulcerating, vegetative, papillomatous lesions occurring on the buccal mucosa and spreading to the skin of the face around the mouth and nose.The regional lymphatics are invaded, and lymphatic invasion to the axillary, inguinal and other nodes of the body is not infrequent. Individual lesions around the mouth and nose are similar to those of mucocutaneous leishmaniasis and yaws, and a differential diagnosis can be obtained only by a laboratory study of material obtained from the lesions.

The lymphangitic type of infection is characterized by massive infection of the lymph nodes of the neck, with no external lesions until necrosis and drainage take place. The portal of entry is probably the mouth, with direct infection of the lymphoid tissue without mucosal lesions.

Visceral infection takes place through the intestinal tract, as evidenced by numerous lesions in the lymphoid tissues of the intestine. Massive infection of the lymph nodes throughout the viscera, enlargement of the spleen and liver and other organs and dissemination of the fungus throughout the body produce a highly fatal form of the disease.

Clinically, this disease differs from North American blastomycosis in that the portal of entry is the mouth, that the intestines are often infected and that in only 15 to 20 per cent of the cases are the lungs involved; in Gilchrist's disease the portal of entry is the respiratory tract or skin, the intestines are not infected and, in the systemic cases, 95 per cent have lung lesions.

Early reports from South America have stated that this disease is invariably fatal. Iodides have occasionally been employed with some success, but their use usually causes the lesions to spread. In view of the effect of iodides in hypersensitive cases of North American blastomycosis, the use of a desensitizing vaccine before iodide treatment in the South American disease seems indicated. Recent reports have shown that the sulfonamides give almost immediate relief, with slow healing of the lesions. These drugs must be given in daily doses over long periods of time — in some cases as long as one to two years.

South American blastomycosis was described first in its cutaneous form by Lutz[116] and Carini[117] in 1908. The first generalized infection was recognized by Splendore,[118] who[119] later named the fungus *Zymonema brasiliense*. For a period of years this fungus was thought to be identical with *Coccidioides immitis*.[120–123] In 1930, however, Almeida[124] showed by comparative studies of material obtained from cases of coccidioidomycosis occurring in the United States and material obtained from Brazilian cases that the two diseases were different. He named the South American fungus *P. brasiliensis*. The cases of coccidioidomycosis reported from South America, therefore, were cases of blastomycosis caused by the multiple-budding Paracoccidioides that had been mistaken for the nonbudding, endosporulating coccidioides. Only three cases of coccidioidomycosis have occurred in South America: Posadas[125] described the disease from Buenos Aires in 1892 but failed to name the fungus; Fonseca[126] reported a case from the Chaco of Argentina in 1928 but named the fungus *Pseudococcidioides mazzai*; and Negroni and Villafane Lastra[126] reported a case from Serrezuela, Province of Cordoba, also in Argentina, in 1939, but named the fungus *Trichosporon proteolyticum*.

The South American disease is said to be caused by three distinct species of Paracoccidioides — *P. brasiliensis* (Almeida[124]), *P. cerebriformis* (Moore[127]) and *P. tenuis* (Moore[128]). Several investigators,[129–131] however, would reduce these species to synonymy, and Conant and Howell[132] would place them all in the genus Blastomyces as a single species, *B. brasiliensis*.

Cryptococcosis

Cryptococcosis (European blastomycosis, Busse–Buschke's disease, torulosis or Torula meningitis) is a subacute or chronic granulomatous infection of man and animals caused by *Cryptococcus neoformans*. This disease may be divided into cutaneous and systemic forms of infection, with the latter always terminating in meningitis because of the marked predilection of the fungus for nervous tissue.

C. neoformans appears in tissue, exudates, sputum and spinal fluid as a large, round, thick-walled budding organism surrounded by a thick capsule. In culture, at any temperature, the fungus remains yeastlike, mucoid, glistening and tan to dark brown. The same type of budding cells with wide capsules are found in cultures as in material from lesions.

Cutaneous cryptococcosis is characterized by acneform pustules that may ulcerate, granuloma-like ulcers, subcutaneous tumors or deep-seated abscesses that may develop anywhere on the body — cheek, neck, abdomen, thigh and groin. Such lesions are usually followed by cerebrospinal involvement or a generalized infection.

Infection of the central nervous system is characterized by protean clinical symptoms — headache, dizziness or faintness, convulsions, nausea and vomiting and signs of increased meningeal irritation with stiffness of the neck and positive Kernig and Brudzinski signs. The spinal-fluid pressure is increased, the cell count is high, and the globulin and albumin are increased, but the sugar content is low. A differential diagnosis would include tuberculous meningitis, syphilis, encephalitis, brain abscess, brain tumor and central-nervous-system degeneration.

Lung infections resemble tuberculosis or a neoplasm by x-ray examination, and diagnosis can be made only by finding the fungus in the sputum by direct examination or by culture.

India-ink preparations of gummy, blood-stained exudates from subcutaneous tumors, abscesses or ulcerations and sputum and wet Giemsa stains of frozen sections provide the best means of demonstrating *C. neoformans* in such materials. The spinal fluid should be centrifuged, and the sediment examined by the India-ink method. Such examinations reveal the round, thick-walled budding fungus surrounded by its characteristic and diagnostic wide gelatinous capsule.

Treatment of cutaneous cryptococcosis has not been too successful, and the disease usually terminates fatally with meningitis. Kessel and Holtzwart[133] reported a successful cure by oral iodides and x-ray treatment to individual lesions on the right and left breasts and amputation of a leg with a knee lesion that failed to heal. Dienst[134] reported a cure after oral iodides and x-ray treatment of a subcutaneous tumor attached to the tenth rib on the right side.

Central-nervous-system cryptococcosis has had a high mortality, not only because the diagnosis has not always been readily apparent, but also because there seemed to be no specific drug. Recent reports, however, have shown that the sulfonamides may be effective. Reeves, Butt and Hammack[135] reported recovery after treatment with sulfapyridine, and Marshall and Teed[136] reported recovery of a patient after treatment with sulfadiazine. Conant et al.[137] have reported a cure of a lung infection after sulfadiazine administration. These reports are a contradiction to the in-vitro studies of Keeney et al.[138] in which sodium sulfathiazole, sodium sulfadiazine and sodium sulfamerazine showed no effect on the growth of *C. neoformans* in culture. What part penicillin will eventually play in the treatment of this disease can be determined only after clinical trial. Keeney et al.[139] report no effect on the fungus in vitro, but Dawson et al.[140] report a killing effect comparable to that of *Staphylococcus aureus*. Jones and Klinck,[141] however, have reported a case in which both sodium sulfadiazine and penicillin were of no value. Also, in-vitro experiments with cultures and in-vivo experiments with mice showed both these drugs to have no effect.

That cryptococcosis as it occurs in this country is the same as Busse–Buschke's disease[142, 143] (European blastomycosis) cannot be doubted, since Benham[144] showed the identity of the etiologic agents. The disease is world-wide in distribution, and the fungus is the same regardless of the type of case from which it is isolated.

C. neoformans was first isolated under natural conditions from peaches by Sanfelice.[145] It has been isolated from animals: Sanfelice[145–147] obtained *S. lithogenes* from an ox and *S. granulomatogenes* from swine, Frothingham[148] *Torula sp.* from a horse, Harrison[149] *T. nasalis* from a horse, and Weidman and Ratcliffe[150] *T. histolytica* from a cheetah. Although the fungus has been isolated from nature and animals, there have been no reports of a natural infection or of transmission from animal to man. The portal of entry in man is thought to be the skin, respiratory tract or intestinal tract. Weis,[151] who compared *C. neoformans* with a species of Blastomyces (*T. klein*) isolated from milk by Klein,[152] suggests that the intestine can, at times, be the portal of entry.

Histoplasmosis

Histoplasmosis (Darling's disease or reticuloendothelial cytomycosis) is an infection of the endothelial cells of the reticuloendothelial system by *Histoplasma capsulatum*. Because of the intracellular distribution of the fungus throughout the body by such a system, the organism resembles *Leishmania donovani* and the disease resembles kala-azar.

H. capsulatum appears in the mononuclear or polymorphonuclear cells of peripheral blood smears, sternal bone-marrow smears, splenic-pulp smears and in tissue sections as a small, oval, sometimes budding cell 1 to 5 microns in diameter. Cultures of such materials on blood agar at incubator temperature develop the small, budding, yeastlike cells. Cultures grown at room temperature, however, develop a filamentous moldlike colony, which may be identified by the characteristic large tuberculate chlamydospores produced from the filaments.

Darling's original description of the disease stated that fever, anemia, leukopenia, splenomegaly, hepatomegaly and emaciation were the outstanding symptoms. Such symptoms may also be those of kala-azar. With the increasing number of cases described within the past few years, it has become evident that the symptomatology varies considerably. Marked lymphadenopathy may necessitate a differential diagnosis to include Hodgkin's disease, lymphosarcoma and aplastic anemia. Many patients have shown ulceration of the tongue, pharynx or larynx and ulceration of the mucosa of the nose that might be mistaken for carcinoma. Several types of skin lesions have been described — papular eruptions, deep punched-out ulcers, petechial hemorrhages and bullous lesions. In the lungs, the parenchymal changes and scattered miliary

lesions may be typical of tuberculosis. Symptoms referable to the intestinal tract are diarrhea, hemorrhage and vomiting, with frequent ulceration of the lymphoid tissue found at autopsy.

Treatment of this disease has not been successful in spite of the use of a wide variety of drugs.[153]

Histoplasmosis was first described by Darling[154–156] from the Canal Zone and considered to be a tropical disease caused by a protozoan, *H. capsulatum*, closely related to the Leishman–Donovan bodies reported in cases of kala-azar. Rocha–Lima[157] reported the occurrence of budding by these organisms and hence considered them to be a fungus, Cryptococcus. Hansmann and Schenken[158, 159] in 1933 and 1934 and DeMonbreun[160] in 1934 were able to culture the organism and definitely proved that it was a fungus. Since then, numerous cases have been described, showing the disease to have a world-wide temperate and subtropical distribution, with the majority of cases occurring within the United States. Meleney[161] reviewed 32 cases up to 1940, and at the present time 74 cases have been reported. The recent excellent review by Parsons and Zarafonetis[153] discusses 71 of these. In this publication may be found the best discussion of the disease to date.

Actinomycosis

Actinomycosis is a chronic suppurative, purulogranulomatous type of infection characterized by the formation of multiple draining sinuses and caused by a single anaerobic species of Actinomyces, *A. bovis*, and several aerobic species of Nocardia (Actinomyces).

Such fungi appear in the tissues, sinus walls or pus as macroscopic granules, which may be yellowish-white, red or black. Microscopically, these granules are composed of a tangled mass of delicate (1 micron in diameter) branching filaments, which are sometimes terminated at the periphery of the granule by broad sheaths, giving the appearance of clubs. When stained by Gram's method, the filaments are gram-positive, and the sheaths, gram-negative; in some species the filaments are also acid-fast.

Cervicofacial actinomycosis, caused by *A. bovis*, is probably the most frequent clinical type of the disease. There is usually a previous history of tooth extraction or infection referable to the teeth followed, after varying periods of time, by a direct extension of an infection through the tissues of the lower jaw and neck. Extensive cellular infiltration of the lesion produces a tumor-like hard mass, from which abscesses rupture, leaving multiple draining sinuses. The sanguinopurulent pus draining from such sinuses contains the characteristic granules. Occasional extension of the infection to the cranial cavity results in brain abscesses.

Pulmonary actinomycosis is characterized by the chronicity of the infection, often with minimal symptoms. Cough, low-grade fever, malaise and loss of weight are the usual findings. X-ray films of the lungs may be typical of tuberculosis with apical lesions or may suggest neoplasm with a hilar mass, but usually the infection is confined to the lower half of the lungs. Involvement of the pleura with effusion, adhesions and thickening is often found in advanced cases. The ribs are frequently invaded. The diagnosis may not become apparent until direct extension of the infection to the thoracic wall produces abscess formation and draining sinuses, from which the granules are recovered.

Metastatic cerebral abscesses or meningitis is a frequent complication of primary lung infection. Actinomycosis of the central nervous system usually does not present symptoms referable to a distinct clinical entity. Spontaneous remissions, however, are more frequent in this disease than in those caused by bacteria.

Abdominal actinomycosis usually originates in the region of the appendix and cecum, presenting the picture of subacute appendicitis. Often the disease follows appendectomy, with failure of the scar to heal completely or a breaking through of a sinus in the old scar or in the region of the navel. Irregular tender abdominal masses may be felt; the viscera usually become infected, as do the vertebral bodies of the spinal column. Until a sinus or sinuses appear in the abdominal wall or groin that drain pus containing the granules, these abdominal lesions present difficult diagnostic problems.

Actinomycotic infections of the limbs (mycetoma) are caused by aerobic species of Nocardia (Actinomyces). The infected foot, knee, hand or arm becomes swollen and deformed, with abscess formation and draining sinuses appearing throughout the mass. In this type of infection the granules may be colored (red or black) in contrast to the sulfur-colored granule of *A. bovis*. Several species may cause such a disease — *N. asteroides*, *N. brasiliensis*, *N. mexicanus*, *N. madurae*, *N. paraguayensis* and *N. pelletieri*. These species are identified by their reactions on milk, gelatin, serum and tyrosinase agar, type of growth on Czapek's agar and Sabouraud's agar, production of pigment, odor and, finally, their microscopic morphology and staining reactions (some are acid-fast). *N. asteroides* has been isolated not only from mycetoma but also from cases of diffuse peritonitis, of pseudotuberculosis with cerebrospinal meningitis and of brain abscess.

Treatment of actinomycosis by adequate surgical drainage combined with x-ray therapy and iodides has proved successful, particularly in cervicofacial infections. With the advent of sulfonamides and penicillin, more specific drugs may now be used with surgical drainage to combat the more difficult thoracic and abdominal cases. The sulfonamides and penicillin may act only against secondary bacterial infections and allow more radical surgery. Cutting and Gebhardt,[162] however, showed sulfathiazole and

sulfadiazine to have some inhibiting effect on the growth of *A. hominis*. Benbow, Smith and Grimson[163] reported excellent results with sulfadiazine and iodides in pulmonary actinomycosis caused by *N. asteroides*. Keeney et al.[139] have shown penicillin to be effective against *A. bovis* in culture.

Cultures should be attempted in every case to determine the type of infecting fungus, aerobic or anaerobic. Cultivation of infected materials on common bacteriologic media and Sabouraud's agar is sufficient to isolate the aerobic species. The anaerobic *A. bovis*, however, can be isolated only by more exacting methods. Rosebury, Epps and Clark[164] used brain-heart-infusion agar plates, to allow streaking and subsequent picking of well isolated colonies. Such plates were incubated in anaerobic jars in the presence of 5 per cent carbon dioxide. Although shake agar cultures, chopped-meat medium and dextrose broth may also be used successfully with uncontaminated materials, the above method of culture is superior when contaminants are present.

The source of infection with *A. bovis* is endogenous. Several reports of the cultivation of this fungus from tonsillar crypts and carious teeth have established the human mouth as the habitat of this anaerobic species.[165–174] Gordan and Hagan[175] were able to cultivate aerobic acid-fast Nocardia (Actinomyces) from soil samples and to show one to be pathogenic for rabbits. The pathogenic aerobic species, therefore, probably occur in the soil and are introduced into the body through the skin (mycetoma) or through the respiratory tract or intestine (systemic).

Moniliasis

Of all the mycotic infections, moniliasis is the most difficult to prove by clinical or laboratory methods. Species of the genus Candida (Monilia) have been isolated from normal mouths,[176] normal intestinal tracts,[177, 178] the vagina[179, 180] and the skin.[177] Such fungi can be found in the sputum of recognized pulmonary diseases, such as tuberculosis and carcinoma. They are also found in the stools from diseases in which diarrhea is a symptom, such as sprue[181] and pernicious anemia.[182] The prevalence of these fungi in normal conditions and diseases in which other etiologic agents are known to be the cause makes the diagnosis of moniliasis possible only by exclusion.

Species of Candida appear in clinical materials as small, oval budding cells with occasional mycelial elements. They are gram-positive when stained by Gram's method. In culture on Sabouraud's medium they develop smooth, white, yeast-like colonies, with oval budding cells on the surface and a mycelium penetrating the agar. Such cultures have a distinct yeasty odor. Only a single species, *Candida* (*Monilia*) *albicans*, is pathogenic.

C. albicans may be the primary cause of disease in a number of clinically recognized conditions. Thrush, or infection of the mucous membranes of the mouth, is encountered more frequently in children than in adults. On the mucosa of the mouth are found extensive or scattered creamy white patches that reveal, on microscopic examination, the budding cells and mycelial elements of Candida.

Perlèche is an infection of the corners of the mouth characterized by macerated, eroded or fissured lesions from which *C. albicans* can be isolated. Such lesions, however, may be associated with a dietary deficiency, and the fungus, which can be found in normal mouths, may be a secondary contaminant.

Vulvovaginitis is a thrushlike infection of the vaginal mucosa and vulva characterized by irritation, pruritus and discharge. The fungus can be found in smears from the vagina and vulva or cultured from swabs used to collect material from the vagina. Pregnancy and diabetes are predisposing factors in the occurrence of this disease.

Infection of the skin by *C. albicans*, except in systemic infections, is usually confined to areas where closely approximating parts cause, with the aid of perspiration, mechanical irritation and maceration of the tissues. Intertrigo of the axillas, inguinal region and inframammary areas is characterized by erythematous, exudative lesions with sharply marginated vesicular or papulosquamous borders. Obesity may be a predisposing factor aiding infection in all the mentioned areas, lactation a factor in the inframammary areas, and diabetes a factor in the intergluteal region. Intertriginous lesions are frequent in dishwashers and others who find it necessary to keep their hands immersed in water over long periods of time.

Onychia and paronychia are often caused by *C. albicans*, being characterized by thickened, grooved, sometimes discolored nails with painful paronychial swellings. Microscopic examination of scrapings in potassium hydroxide preparations reveals the budding yeastlike cells.

Bronchomoniliasis is characterized by a persistent cough, mucoid sputum with white flakes composed of cellular debris and yeastlike cells, a few scattered rales at the lung bases and x-ray films showing a slight to moderate peribronchial thickening. A more extensive invasion of the lungs, producing pulmonary moniliasis, is sometimes indistinguishable from tuberculosis. Malaise, fever, night sweats, chest pain, dyspnea, cough and hemoptysis, with signs of pleural thickening and consolidation, are not unusual. The disease may be acute, with rapid onset, or chronic, with frequent remissions and exacerbations.

Systemic infections are rare but do occur following prolonged refractory stomatitis, glossitis or resistant infections of the skin, particularly in the debilitated patient. Rockwood and Greenwood[183] and Miale[184] have reported 2 fatal cases, with autopsy findings. In Miale's case and another reported by

Smith and Sano,[185] the central nervous system was involved.

Mycotic endocarditis caused by species of Candida have been reported in drug addicts by Joachim and Polayes[186] and Wikler and his associates.[187] These cases, however, yielded cultures of *C. parakrusei* and *C. Guillermondi*, two species considered to be nonpathogenic.

The possible role of the yeastlike fungi in the pathogenesis of the diseases from which they had been isolated could not be determined until standard methods of classification allowed these organisms to be identified. Hundreds of species differing but slightly from each other have been reported in the medical literature, and until recently, attempts to classify them have resulted in confusion. Comparative studies of cultures by Benham,[188] Martin et al.,[189] Martin and Jones[190] and Langeron and Guerra[191] have succeeded in reducing the vast number of reported species to a few well described organisms. These methods can be used to identify quickly and easily yeastlike organisms isolated from any infectious process. The reported incidence of a yeastlike fungus, if identified accurately according to these methods, now has meaning, and the previous confusion regarding their ability to cause disease should be lessened.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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CASE 31321

PRESENTATION OF CASE

A thirty-one-year-old man was admitted to the hospital complaining of weakness, nausea and vomiting.

Five days before admission he slipped on the bottom step of a stairway, falling heavily on the left elbow and the left side of the thoracic cage. The patient's left ribs were strapped, and he was later sent to the emergency ward of this hospital, where he spent the night. The following morning he was fairly comfortable and was discharged. At home he did not feel well, complaining of profuse perspiration, of progressive weakness and of pain in the left thoracic cage. On the day before admission, malaise, nausea and intermittent vomiting appeared. On the day of admission the vomiting recurred. He complained of hiccoughs and of pain in the left upper quadrant of the abdomen and in the left shoulder.

The patient was well developed and well nourished, slightly icteric and in acute distress. The skin was cold and somewhat clammy. The heart and lungs were normal. The abdomen was soft, with no spasm or rebound tenderness, but there was tenderness in the left upper quadrant. There was no definite fluid wave or shifting dullness.

The temperature was 98°F., the pulse 100, and the respirations 25. The blood pressure was 110 systolic, 70 diastolic.

The red-cell count was 2,500,000, and the white-cell count 10,000. The icteric index was 15. A flat plate of the abdomen showed that the stomach was full of air. The splenic shadow was much larger than usual, and the lateral wall of the stomach was slightly serrated. There was no fracture of the ribs overlying the spleen. There were no dilated loops of bowel. Some gas was present in the sigmoid.

Soon after admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CARROLL MILLER: Several points in this patient's story are likely to be confusing to the first observers of such a case. The patient stressed a blow to the left side of the chest, and he had pain in that region. Naturally when an examiner sees such a patient in the Emergency Ward or at home he thinks immediately of broken ribs, and the obvious treatment for such a condition is strapping to immobilize the broken parts. In addition to pain this patient had weakness, nausea and vomiting. Unless a person is relatively susceptible to pain, a blow in the lower chest does not cause these symptoms, and one must therefore think of other conditions to explain them. I should be interested to know if any blood studies were done when the patient first came into the Emergency Ward.

DR. BENJAMIN CASTLEMAN: None are recorded.

DR. MILLER: He apparently came into the Emergency Ward fairly soon after the accident. He felt reasonably comfortable the next morning and went home. Weakness persisted, however, and he complained of profuse perspiration. In the light of what must have been subsequently found we can explain these symptoms. He began to have malaise, nausea and vomiting. Then, as the condition progressed, he had hiccoughs and pain in the left upper quadrant of the abdomen — a slight shift downward from the chest — and in the left shoulder. When there is trauma to this part of the body one thinks first of injury to the spleen; of course, other viscera that may be injured in that region are the splenic flexure of the colon, the stomach and the kidney. We know that it takes a fairly severe blow to cause a rupture of a hollow viscus and also a reasonably severe blow to cause sufficient contusion or rupture of the kidney to produce symptoms in that region. It may, however, take only an extremely slight blow to cause a laceration or rupture of the spleen.

So far as physical signs are concerned, he must have been pale, although it does not say so in the account of the case. He was slightly icteric, cold, somewhat clammy and definitely sick. These signs go only with what might be called mild shock. The pulse was up a bit, and the blood pressure was perhaps slightly lower than that which a man of his age and condition should have. The positive findings on examination consisted mainly of tenderness in the left upper quadrant of the abdomen. There was no fluid wave or shifting dullness. The laboratory tests showed a marked reduction in the number of red cells, and the white cells were slightly elevated. The icteric index was definitely elevated. A flat plate of the abdomen in such a condition is of considerable interest, and I think that we might see the x-ray films at this point. In such films one should first attempt to demonstrate air under the diaphragm, indicating leakage from a hollow viscus, and then signs of fluid, although these are frequently not easily recognized in the ordinary flat film.

DR. MILFORD D. SCHULZ: The diaphragm is not shown on these films. I do not know whether there is air beneath it, but there certainly is no evidence of air in the peritoneal cavity. The stomach is full of air, and there is some serration of its lateral margin. The lower pole of the spleen is large and round.

*On leave of absence

I cannot trace the splenic shadow upward. I cannot see the edge of the liver. I might point out that one femoral head is deformed.

DR. MILLER: Apparently an old process?

DR. SCHULZ: Yes.

DR. MILLER: Would you say that the splenic flexure of the colon is lower than usual?

DR. SCHULZ: I do not know: I cannot see it.

DR. MILLER: Another condition that I did not mention in association with intra-abdominal injuries is rupture of the liver, which is less likely with injury of the left side of the abdomen than it is with injury of the right side. *Contrecoup* rupture, however, does occur.

My presumptive diagnosis in this case is a delayed rupture of the spleen. We have evidence for this both from the clinical findings and from the statistics reported in the literature. There was an increase in the size of the splenic shadow. Dr. Schulz has pointed out the lower border of the spleen, but there seems to be further density medial to the spleen, pushing the stomach a little more to the midline than it ordinarily would be. The course of events in this case is quite typical. Immediate rupture of the spleen usually follows a fairly severe injury. Late rupture may occur within a week and sometimes even later. It is said that 50 per cent of the delayed ruptures take place within the first week and that an additional 25 per cent occur within a two-week period after injury.

How can one explain a late rupture? Usually it is due to subcapsular contusion followed by breaking up of the splenic pulp, hemorrhage beneath the capsule and gradual stretching, with increasing tension of the capsule until the capsule breaks and releases both the accumulated and fresh blood. There may be a rupture of the capsule at the time of the first injury, but because of certain clotting mechanisms, thrombi form in the region of the spleen, which seal off all the viscera locally, thus preventing spread into the rest of the abdomen. No shifting dullness or free fluid in the abdomen was found on physical examination. The icteric index may have been increased because of the absorption of hemoglobin from the peritoneal cavity or from spleen, which might have had an accumulation of hemolyzed blood within the splenic capsule. There apparently was no intrathoracic disease, and no fluid was demonstrated either by physical or by x-ray examination. There was no fracture of the ribs overlying the spleen. Of course, one must always suspect fracture of the ribs, with puncture of the pleura and an accumulation of intrapleural blood, when there is a complaint of weakness and pain in the left side following an injury.

I think that the important point, presuming my diagnosis to be correct, is that it is easy to skip over such a case lightly and to discharge the patient home, permitting him to carry on full activity after a few days. We have had several cases within recent years in which such an injury has been sustained; these patients have to be watched carefully for the development of symptoms. It is important to remember that splenic rupture can occur late, and that when it does it may be one of the most acute abdominal emergencies that we see. The patient must be operated on immediately, and even in case of doubt, an exploratory laparotomy is warranted.

I shall close my discussion by saying that this patient had a traumatized spleen, probably a subcapsular contusion, at the time of injury, which about five days later ruptured into the peritoneal cavity producing nausea and vomiting; in other words, he had a delayed rupture of the spleen.

I neglected to ask about a urinalysis at the time of admission.

DR. CASTLEMAN: It was negative.

Have you anything further to say about the x-ray films, Dr. Sosman?

DR. M. C. SOSMAN: I should say that the patient had an enlarged spleen, which displaced the stomach upward and medially. A ruptured spleen is a logical diagnosis, with hemorrhage into or around the spleen, or both.

DR. EDWARD HAMLIN, JR.: I saw this patient fifteen minutes before operation. At that time he had definite shifting dullness. At operation the spleen was four to five times its normal size. It was soft and mushy and somewhat larger than one would expect from just intrasplenic hemorrhage. It was easy to remove.

DR. CASTLEMAN: Was there a large amount of free blood in the abdomen?

DR. HAMLIN: A great deal.

CLINICAL DIAGNOSIS

Ruptured spleen.

DR. MILLER'S DIAGNOSIS

Delayed rupture of spleen.

ANATOMICAL DIAGNOSES

Gaucher's disease.
Ruptured spleen.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The spleen that we received weighed 800 gm. and contained three tears — one on the upper pole, one on the medial surface and one on the posterior aspect. The largest, the one on the medial surface, was 9 cm. in length and 1 cm. in depth. The surface was otherwise smooth. The cut surface was brick red except for several well circumscribed hemorrhagic areas, measuring 1 or 2 cm. in diameter, scattered throughout the parenchyma, not necessarily close to the capsule. We were not able to find any really large hematomas beneath the capsule. We thought that it was an ab-

normal spleen but could not pin a definite diagnosis on it grossly. It did not look like a Banti spleen, and it was not hard enough; but it did suggest the spleen of hemolytic jaundice. Sections, however, showed the characteristic histologic picture of Gaucher's disease. Throughout the pulp there were numerous large foamy slightly granular cells with small round pyknotic nuclei (Fig. 1). The follicles were reduced in number, owing to replacement by the Gaucher cells, which, as you may recall, are reticulum cells filled with kerasin, — one of the cerebrosides. The one clue to the diagnosis was in the x-ray film of the femoral head. Dr. Schulz, will you show the films taken after the diagnosis was established?

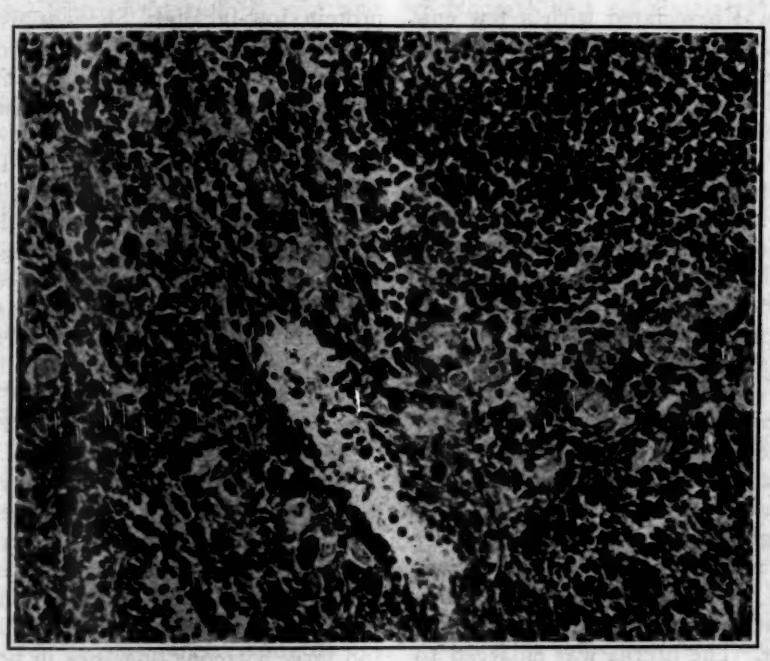

FIGURE 1. *Photomicrograph of Spleen Showing the Large Number of Gaucher Cells. Note the absence of Gaucher material in the endothelial cells lining the sinusoids.*

DR. SCHULZ: The films taken after operation show deformity of one femoral head. The medullary canals of the femurs and humerus are widened at the expense of the cortices. The lower ends of the femurs show the Erlenmeyer-flask deformity, which is quite typical.

DR. CASTLEMAN: This disease usually occurs in young persons. This man was thirty-one, but it has been reported in people over fifty. I believe that a large percentage of the cases have occurred in Jews, and this man was a Jew.

It is possible that these bone lesions, which are produced by the Gaucher cells within the marrow and not in the cortex, may increase in number. A number of cases have been reported in which bone lesions first appeared following splenectomy.*

This patient is doing well and is about to go home.

*Pick, L. Classification of diseases of lipoid metabolism and Gaucher's disease. *Am. J. M. Sc.* 185:453-469, 1933.

CASE 31322

PRESENTATION OF CASE

First admission. A twenty-year-old housewife was admitted to the hospital complaining of abdominal pain and jaundice.

About nine months before admission the patient was referred to the Out Patient Department following one positive and one doubtful premarital Hinton test. Her fiance was Hinton negative, and she admitted no other exposure. She denied having had any of the stigmas of acquired or congenital syphilis. The patient's mother and sister had had tuberculosis, but there was no family history of syphilis or positive serologic tests. At that time, physical examination revealed nothing remarkable. Repeated Hinton tests were positive. One Wassermann test was positive, and another was questionable. A Wassermann test on the spinal fluid was negative. The patient was started on a course of antisyphilitic therapy. She had no ill effects from bismuth, but when Mapharsen was begun she complained of nausea without vomiting beginning about half an hour after each treatment and lasting for about two hours. She had no diarrhea or itching, and the stools and urine remained normal. Neoarsphenamine was

substituted for Mapharsen and caused some nausea until the dosage was reduced, after which there were no ill effects. While under treatment she had married, and six months before entry had become pregnant. Eight days before admission she ate some fried sea food and on the following day developed a constant sharp pain in the epigastrium and right upper quadrant. Nausea developed simultaneously with the pain, and was associated with a few episodes of vomiting dark-green material. Three days before admission the pain became severe and the skin and scleras were observed to be jaundiced. She developed constipation, her bowel movements having been normal until that time. The urine became dark. She felt feverish and had a temperature of 101 to 102°F. During the following three days the pain and jaundice subsided somewhat but the discomfort in the right upper quadrant remained.

Physical examination showed a well developed, well nourished, poorly hydrated, sick-appearing woman. The skin was hot and dry. A few blotchy red spots were observed over the face and palms of the hands. There was no definite jaundice, but the peripheries of the scleras had a questionable yellowish tint. The heart and lungs were not remarkable. The abdomen revealed moderate tenderness and slight spasm in the right upper quadrant. The upper margin of the liver was at the fifth rib, and the lower margin 5 cm. below the costal margin in the midclavicular line. Neither the spleen nor the gall bladder could be felt. The uterus was enlarged to occupy two thirds of the distance from the symphysis pubis to the umbilicus. Fetal motions and heart sounds were present. The pregnancy was estimated to be of six months' duration. Pelvic examination revealed moderate tenderness but was otherwise negative.

The temperature was 98.6°F., the pulse 100, and the respirations 22. The blood pressure was 118 systolic, 85 diastolic.

Examination of the blood showed a red-cell count of 4,310,000, with 10.5 gm. of hemoglobin, and a white-cell count of 19,300, with 80 per cent neutrophils. The urine had a specific gravity of 1.018, subsequently ranging from 1.002 to 1.014; the sediment contained 3 to 4 white cells per high-power field. The urine gave a positive test for urobilinogen in a dilution of 1:8. One week later it was present in a dilution of 1:64, and following this it was positive three times in a dilution of 1:16. The serum nonprotein nitrogen was 21.5 mg. per 100 cc., the phosphorus 2.6 mg., the protein 5.88 gm., the albumin 3.33 gm. and the globulin 2.55 gm. (an albumin-globulin ratio of 1.3), the alkaline phosphatase 4.2 Bodansky units, and the chloride 106 milliequiv. per liter. A bromsulfalein test (5 mg. per kilogram) showed retention of 60 per cent of the dye after forty-five minutes. A cephalin-flocculation test was negative in twenty-four hours but questionably positive after forty-eight hours. The van den Bergh test was 0.85 mg. direct and 1.2 mg. indirect. The prothrombin time was 17 seconds (normal, 18 to 20 seconds).

X-ray examination of the abdomen revealed a uterus enlarged to the third lumbar vertebra. The liver appeared normal in size. No gallstones were observed.

The patient was put on a high-carbohydrate, high-protein, low-fat diet. She was given vitamins intravenously and allowed fluids up to 2500 cc. per day. She received two injections of bismuth within the fourteen days following admission. The urinary sediment continued to show a few white cells. The red-cell count fell to 3,300,000. The blood pressure, temperature and pulse remained in a normal range. At that time, a cephalin-flocculation test gave a doubtful reaction after forty-eight hours and the van den Bergh test was reported as normal. The patient felt better. The liver was only 3 cm. below the costal margin and was much less tender than at first. The blotchy lesions on the hands and face improved, but the scleras remained "muddy." Bismuth injections were stopped, and a course of penicillin (1,200,000 units) was substituted.

On the nineteenth hospital day, following the injection of 1500 cc. of 10 per cent dextrose in water with the addition of nicotinamide, thiamine chloride, riboflavin, Hykinone and cevitamic acid, the patient complained of weakness and blurred yellow vision. There was edema of lids, as well as chemosis and large vitreous opacities in both eyes. She had a recurrence of the anorexia, malaise and slight liver tenderness. Her face became swollen and pale. These symptoms persisted. The fetus remained normal, with a strong heart beat at a rate of 144 per minute.

On the twenty-first hospital day the patient was discharged to a lying-in hospital. The blood pressure had risen from 130 systolic, 90 diastolic, to 150 systolic, 115 diastolic, and the urine gave a + test for albumin on the last two examinations.

Final admission (two weeks later). In the interim, labor had been induced at the lying-in hospital following the development of convulsions. She was delivered of a nonsyphilitic infant who lived only twenty hours. Following delivery, the patient developed fever, leukocytosis and pyuria. Two days before admission, she had a shaking chill, associated with a white-cell count of 50,000. On the day before admission she had one episode of vomiting.

On examination the patient was pale and thin. There were a few slightly erythematous lesions on the face. The eyes showed no residual chemosis. The fundi were pale but otherwise normal. The pharynx was slightly reddened and edematous. The heart and lungs were normal. The liver was tender and extended four fingerbreadths below the costal margin. There was no true spasm of the abdominal wall, but exquisite tenderness elicited in the right costovertebral angle. The uterus was well contracted.

The temperature was 105°F., the pulse 144, and the respirations 25. The blood pressure was 100 systolic, 65 diastolic.

Examination of the blood showed a red-cell count of 2,550,000, with 7.5 gm. of hemoglobin, and a white-cell count of 42,000, with 67 per cent mature neutrophils, 23 per cent band forms, 8 per cent lymphocytes, 1 per cent myelocytes and 1 per cent monocytes. The red cells were hypochromic and normocytic, with moderate variation in size and shape. The urine had a specific gravity of 1.007 and gave a +++ test for albumin; the sediment contained 2 to 3 red cells and innumerable white cells per high-power field. Culture revealed abundant colonies of colon bacillus. A stool gave a ++ guaiac test. The urine was positive for urobilinogen in a dilution of 1:32. The nonprotein nitrogen was 21.5 mg. per 100 cc., the protein 5.95 gm., the albumin 3.52 gm., the globulin 2.43 gm., the chloride 100 milliequiv. per liter, the van den Bergh normal, and the prothrombin time 29 seconds. Repeated Hinton tests were negative in all dilutions. The cephalin-flocculation test was negative after twenty-four hours and ++ after forty-eight hours.

The patient was put on a course of intensive vitamin and carbohydrate therapy. She was treated with small amounts of sulfadiazine. The temperature responded for a few days and then rose again to 104°F. She began to vomit frequently. The urinary intake and output were poor. The liver tenderness and costovertebral angle pain increased in severity. The liver became larger, and the abdomen became distended. Peristalsis could hardly be distinguished. There was shifting dullness, without definite fluid wave. The temperature spiked at least once a day, often rising to 104°F. Pelvic and rectal examinations were negative. X-ray examination revealed hepatomegaly and a suggestion of abdominal fluid.

On the eleventh hospital day the patient became mildly disoriented. She had a chill, and the temperature spiked to 104.8°F. On the thirteenth hospital day she complained of pain and exhibited tenderness in the right groin (femoral triangle), associated with rising temperature, pulse and respirations. On the seventeenth hospital day she had generalized convulsions and was momentarily unresponsive; the trachea filled with a coarse stringy exudate but soon cleared. On the nineteenth hospital day she became incontinent of feces. The pulse was rapid and threadlike, and the pharynx was full of hemorrhagic purulent material. The temperature was 104°F., and the respirations labored and slow. The latter rapidly became slower and then ceased altogether.

Differential Diagnosis

Dr. Earle M. Chapman: This is a long story of a young mother who died at the age of twenty. I should like to go back and reconstruct the story from the beginning as I see it.

In the first place, on the evidence of a positive serologic test for syphilis she was treated with a highly toxic agent, arsenic. I am going to raise a doubt that she had syphilis because the story is not that of syphilis. There was no evidence physically of syphilis, and there were only these fluctuating tests to indicate such disease. I think that the work of Neurath and his associates* at Duke University differentiating positive and false-positive tests for syphilis has been a valuable contribution. Their method has been a great help to me recently in differentiating these cases. Strangely enough, three of my cases have been women in the same category as this. The reports were positive, but by the Neurath method they were shown to be biologically false. This patient we are discussing today, however, was treated with arsenic, and while under treatment, it seems to me that the liver was moderately damaged, not enough to explain her death. They looked vainly by means of repeated tests to determine whether the large and tender liver was sufficiently damaged to explain the outcome. The bromsulfalein test alone was positive; the first time it was done it showed retention of 60 per cent of the dye after forty-five minutes. The dose was quite large — 5 mg. per kilogram. The other tests indicated little damage. It is true that she had a slight degree of jaundice in the beginning, but this can be explained by a moderate arsenical hepatitis.

When we come to the present illness, we find that she had been perfectly well until eight days before admission, when she had abdominal pain, nausea, vomiting and fever, which are signs of acute infection. This sudden episode really is the clue, as I see it, to the cause of death. The record states that she had a rash on the face and hands. Of course that may be a red herring to make us believe that it was recurring secondary syphilis or it may hint that this was lupus erythematosus, but I see nothing in this illness to fit with either diagnosis.

What organ was the one that finally failed? I do not believe, as I have said, that the hepatitis was severe enough. None of the tests fit with cirrhosis of the liver. It is clear, however, that she had kidney trouble. The specific gravity was fixed, and she had albuminuria. The development of eclampsia with convulsions during pregnancy indicates that the kidneys had been damaged. Yet she came back to the hospital and died with a normal nonprotein nitrogen, which clearly shows that the cause of death was not uremia. Although she did not die of primary renal failure, she obviously had an infection in the urinary system.

On the second admission the urinary sediment contained numerous white cells and a culture yielded abundant colonies of colon bacilli. On physical

*Neurath, H., et al. Serological diagnosis of syphilis. *Science* **101**:68, 1945.

examination she was edematous and had exquisite tenderness in the right costovertebral angle. She then continued to have evidence of infection, — I assume she had a septic type of temperature chart,— and she failed to respond to both sulfadiazine and penicillin. When a patient dies without responding to these, there is certainly one complication that has to be considered, namely, undrained pus. None of these chemotherapeutic agents will drain a septic area; that is a surgical procedure.

Dr. Benjamin Castleman: You might like to glance at the temperature chart?

Dr. Chapman: It is just as I supposed; she certainly ran a septic course. Where was the sepsis located?

Going back again, I have to consider that the first attack may have been appendicitis, a frequent disease at this age, and therefore she may have had a pylephlebitis. But the one point that I believe is against pylephlebitis is the fact that the appearance of jaundice in five days favors an intrahepatic type of disease rather than an infectious process from a pylephlebitis. Of course, it may have originally been an inflammatory reaction of the right kidney, such as a perinephric abscess, causing a toxic picture with fever and failure to respond to chemotherapy. That would fit in with the final course, since she had exquisite tenderness in the right costovertebral angle.

There is one laboratory finding that is puzzling me and I cannot fit it into the picture; that is the ++ guaiac test in the stool. The excessively high white-cell counts and the anemia fit in with sepsis arising from pus in the right kidney on top of pyelonephritis, which she had had in a mild way previously, it having been linked with the eclampsia.

Now we come to the final phase of her illness. The history states that the liver increased in size, that the abdomen became distended and that peristalsis was minimal. There again, I think that we all know that kidney disease reflexly can simulate intestinal obstruction: the bowel becomes atonic secondary to renal disease, and that fits into the pattern. Then finally she had these convulsions and was unresponsive and hyperthermia was present — all of which leads one to think of some septic metastatic process in the brain, which I can see no possible way to diagnose.

Dr. Castleman: Dr. FitzHugh, you saw this patient. Will you tell us more about her?

Dr. Greene FitzHugh: We believed that the blood picture and the albumin in the urine indicated a definite toxemia, and that is why we sent her to the lying-in hospital.

Two days after the pregnancy was interrupted, the blood pressure came down and the urine cleared; we then had quite a discussion whether we should give her bismuth, since she already had a damaged liver. At that time antisyphilitic treatment with penicillin had not reached the stage where it was generally accepted. We had considerable discussion about the diagnosis. The syphilologists thought that it was syphilis and that we had better go on with some form of antisyphilitic therapy. So we started with bismuth, but with the reports that began to accumulate on the treatment of syphilis with penicillin, we decided that we could safely shift from bismuth to penicillin.

Dr. John L. Newell: When this patient was admitted to the Massachusetts General Hospital she was six months pregnant. I assume that she was recovering from toxic hepatitis, which was believed to have been caused by arsenical treatment. Then she developed a rather fulminating pre-eclampsia. We know that there is no better way to aggravate a pre-eclampsia than to have large amounts of fluid given intravenously.

I did not see her at the lying-in hospital, but she must have had a rapidly progressive course. I should say from an obstetric point of view that it was fortunate that they were able to induce her at seven months. They certainly did not operate. While at the lying-in hospital, she developed pyelitis, chills and eclampsia, which are commonly associated. In fact it is considered by some men that pyelitis is the etiologic agent. It seems to me that this might have been a pyelonephritis that had progressed to a perinephric abscess and the development of generalized sepsis.

Clinical Diagnoses

Toxic hepatitis.
Pyelonephritis.
Syphilis, latent.

Dr. Chapman's Diagnoses

False-positive test for syphilis?
Arsenical hepatitis.
Eclampsia, ante-partum.
Pyelonephritis.
Perinephric abscess.
Septicemia.
Brain abscess?

Anatomical Diagnoses

Eclampsia.
Infarcts of liver, multiple.
Infarcts of spleen, kidneys, lungs, adrenal gland and brain.
Septicemia, terminal (*Clostridium welchii*).
Septicemia (colon bacillus).
Multiple abscesses: abdominal wound, sternum, left clavicle, liver and adrenal glands.
Focal necroses in liver.
Pyelonephritis, acute.

Pathological Discussion

Dr. Castleman: On the second admission to this hospital the clinicians were not sure of the diagnosis and decided to make a small incision to find

out what was wrong with the liver. They found an enlarged liver; a biopsy showed numerous areas of necrosis and hemorrhagic infarction in the periphery of the liver lobules, findings characteristic of eclampsia. Many of the vessels were thrombosed. In other words, she still had eclampsia when she returned from the lying-in hospital. That, I believe, accounted for the large size of the liver and for all the liver symptoms. Following operation she did not do well, developed sepsis in the operative wound, from which we were able to culture colon bacilli, and died in about two weeks.

At autopsy the liver infarcts were widespread; there was thrombosis of the right hepatic artery, and microscopically thromboses were seen in many of the hepatic veins. The kidneys were tremendous in size, each weighing 350 gm., which is about twice the normal weight. There were numerous thrombi associated with hemorrhagic infarction, as well as old blood within the tubules. We also found tiny thrombi in the brain, with small foci of infarction. Just before she died she developed gas-bacillus infection; by the time we did the autopsy, eleven hours post mortem, gas bubbles were grossly visible and we were able to recover the Welch bacillus from every organ. I believe that was just a terminal event, since colon bacilli had been cultured from the blood before death. I think that we can explain the entire picture on eclampsia associated with a severe renal infection.

DR. CHAPMAN: What about the arsenic?

DR. CASTLEMAN: I do not know; I suppose that a liver previously damaged by arsenic may be more prone to develop eclampsia, although I do not recall ever having heard anything said about it.

DR. NEWELL: I have never heard that.

DR. CASTLEMAN: Of course, no one knows the cause of eclampsia. A toxic agent — whatever it is that starts it off — possibly causes more damage in a diseased liver than it does in a normal one.

DR. NEWELL: I am surprised that this patient apparently recovered clinically from the eclampsia and yet had all these manifestations.

DR. CASTLEMAN: Certainly the appearance of the liver is characteristic of eclampsia. Could it have been post-partum eclampsia?

DR. NEWELL: But she did not die post partum. Death occurred three weeks after the convulsions.

DR. CASTLEMAN: She had convulsions before delivery. Did she have any afterward?

DR. FITZHUGH: She had no post-partum convulsions in the lying-in hospital. She had them before she was delivered and terminally at this hospital.

DR. NEWELL: Do you think that the terminal convulsions were due to eclampsia — after two and a half or three weeks?

DR. CASTLEMAN: I do not know. She had several small lesions in the brain. Certainly the changes in the kidneys and the liver and even in the heart are those that are usually found in eclampsia, but it is possible that they were the result of the original ante-partum eclampsia.

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MEDICAL CARE FOR VETERANS

The failure of the people of the United States in the past to provide the best of medical care for veterans is inexcusable. It has been argued that such care should be limited to conditions or diseases directly or indirectly attributable to military service, but in many cases the line of distinction is difficult to draw and if there is any question the veteran certainly deserves the benefit of the doubt. Furthermore, it seems reasonable that medical and hospital care should be furnished for all veterans, without regard to the cause of their illnesses or disabilities. Now that thousands of wounded are being returned to this country, to be discharged to the care of the Veterans Administration after a certain period in Army and Navy hospitals, its facilities become of increasingly great importance, particularly since there is a possibility that the program will be extended to include the care of their dependents.

The Veterans Administration was created over twenty years ago, and in the intervening period, hundreds of millions of dollars have been turned over to it by Congress for the construction of hospitals, their staffing and their maintenance. In other words, the necessary wherewithal has been provided. Unfortunately, however, this type of medical practice has failed to attract the most competent of the medical profession.

Undoubtedly one of the reasons for this lack of appeal is the fact that physicians of the Veterans Administration are under the control and supervision of men with relatively little knowledge regarding medical matters. Three bills now before Congress (H. R. 3310 and 3317 and S. 1079) propose a department or bureau of medicine and surgery within the Veterans Administration.

Reorganization of the medical personnel along such lines would eliminate some of the difficulties of the past, but the provision that medical officers of the Army and Navy may be detailed for service in the Veterans Administration is an undemocratic maneuver that deserves little support. Rather than resort to compulsion, would it not be better to create a medical organization that appeals to the returning medical officer and to the recent graduate? Each hospital would have medical and surgical heads who are well known and competent in their particular lines of work. Appropriate salaries would be paid, and high-grade investigative work, carried out in well equipped and properly staffed laboratories, would be encouraged. In other words, these hospitals would be comparable with the modern first-class teaching hospital.

The advantages of a setup of this sort are obvious. In the first place, the veteran would receive better medical care than he has ever received in the past. Secondly, medical research would be promoted. Thirdly, hospitals of this type would undoubtedly be approved for internships and residencies, and these facilities, in addition to being attractive to the recent medical graduate, would at

once help considerably in the problem, as yet unsolved, of providing adequate means for the postgraduate training of discharged medical officers. And finally, the ultimate cost to the taxpayer — a matter that appears to receive little or no thought these days — would be decreased.

COSMETICS CONTAINING HORMONES

Cosmetics containing hormones are advertised nationally and are available everywhere for purchase without a prescription by a gullible public. Cosmetics are defined as applications intended to beautify and improve the complexion, skin or hair. They are designed to make a person more attractive, to delay (or perhaps better, to hide) the appearance of the manifestations on the skin of advancing years, to cover defects and, in general, to make the skin softer and more pleasant to look on. The addition of hormones, which are physiologically active ingredients derived from endocrine glands or their synthetic duplicates, alters their status and creates a potentially serious situation. These beautifying preparations then become active and possibly dangerous and should be classed with certain drugs, serums, vaccines, vitamins and other biologic products. As such they should come within the jurisdiction of the United States Pharmacopoeial Convention, the Committee on the National Formulary of the American Pharmaceutical Association or the Council on Pharmacy and Chemistry of the American Medical Association. It is significant that none of these authorities have accepted these hormone-containing preparations.

Extravagant claims are made of the glamorous results of such applications, and enormous sums of money in the aggregate are being spent by ill-advised people lured by such advertisements. There is, however, no satisfactory evidence that justifies the use of hormone-containing cosmetics for the purpose of local beautifying effects. The Federal Food and Drug Administration, as evidenced by a letter from Commissioner Dunbar published elsewhere in this issue of the *Journal*, is "skeptical of the benefits, if any, which accrue from the local use of these products." He adds, "We have consistently informed manufacturers that because of the uncertainty of the ultimate effect of the use of these products and because of their dubious value we do not look with favor upon their distribution for lay use." On the other hand, sufficient absorption from the injudicious use of estrogen-containing cosmetics to upset normal body activities has been demonstrated. Eller and Wolff* have recently reviewed the evidence concerning the absorption of such preparations. In addition, the cancer-promoting properties of estrogenic substances are reasonably well established. Much experimental work must be done to determine all the possible effects of a long-term use of such agents in the average human being, and pending such work, it is well that their use be carefully restricted.

The physician is seldom consulted regarding the use of cosmetics or their composition. He should, however, be cognizant of the fact that there is a lack of convincing data from carefully controlled studies to justify the lurid advertisements of the cosmetic manufacturers.

*Eller, J. J., and Wolff, S. Hormones and vitamins in cosmetics *J. A. M. A.* 114:1865-1875 and 2002-2010, 1940.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DEXTER — Fred F. Dexter, M.D., of Springfield, died on July 10. He was in his sixty-seventh year.

Dr. Dexter received his degree from Harvard Medical School in 1904. Before his retirement twelve years ago, he was a practicing gastroenterologist. He was secretary of the Eastern Hampden Medical Association from 1914 to 1915. He was a fellow of the American Medical Association and a member of the Springfield Academy of Medicine.

His widow survives.

DICKSON — Richard E. Dickson, M.D., of Holyoke, died on May 8. He was in his seventy-eighth year.

Dr. Dickson received his degree from Jefferson Medical College of Philadelphia in 1895. He had served as president of the Eastern Hampden Medical Association and was on the staff of the Holyoke Hospital. He was a fellow of the American Medical Association.

METCALF — Richard Metcalf, M.D., of Winthrop, died on May 21. He was in his fifty-eighth year.

Dr. Metcalf received his degree from Tufts College Medical School in 1913. He was a fellow of the American Medical Association.

His widow survives.

REDDY — Joseph W. Reddy, M.D., of South Boston, died recently. He was in his seventy-fifth year.

Dr. Reddy received his degree from Harvard Medical School in 1896 and retired from active practice in 1940. He was a fellow of the American Medical Association.

CORRESPONDENCE

PHYSICIANS FORUM

To the Editor: Over the years preceding, during and following my incumbency as president of the Massachusetts Medical Society I have been disturbed by what has seemed to me the lack of opportunity for the minority (perhaps the majority) of the members of the Massachusetts Medical Society to present their point of view with a reasonable chance of its receiving appropriate attention. I feel that the same situation exists in the American Medical Association. In certain instances there have even been attempts to suppress the expression of opinion of the minority. How to correct this unfortunate situation has not been clear, but recently an opportunity to improve the situation seems to have developed due to the formation and growth of the Physicians Forum, Incorporated, for the study of medical care, of which I am an active member.

This organization started in New York City a few years ago among members of a county society of the New York Medical Society, who felt that there was need for a method of expressing the opinion of the minority in organized medicine. From its meager beginning it has become a national organization, and on December 8 and 9, 1944, held in Washington, D. C., a National Health Conference on the Problems of Medical Care, which turned out to be a meeting of real significance, with fifty-one organizations represented and many individuals of prominence participating.

The Forum analyzes relevant legislation, publishes bulletins and other literature and appears before organizations of physicians as well as professional and consumers groups, and it has been called upon to advise Congressional committees.

Among other activities the Physicians Forum has now taken up the fight for the passage of the Wagner–Murray–Dingell Bill (S. 1050). The Forum has been asked by lay groups interested in this legislation to assume the leadership of those members in the medical profession who are interested in this important struggle.

Although the Physicians Forum has become national in scope, it is still rather limited in membership in certain areas. Its officers believe that there are many members of the medical profession belonging to their state societies who would welcome this method of expressing a minority (or perhaps majority) opinion. The Forum also believes that there are many members of the medical profession who favor this progressive program for the delivery of medical care to the great masses of American people proposed by the Wagner–Murray–Dingell Bill but are at sea in regard to how to register their feelings.

The Physicians Forum offers such an opportunity. Its membership at the present time is limited to members of county or state societies and the National Medical Association. Those physicians who are interested in joining the Physicians Forum, or who wish to learn more of its activities, may do so by applying to me or to the headquarters of the Physicians Forum at 510 Madison Avenue, New York City.

CHANNING FROTHINGHAM, M.D.
1153 Centre Street
Jamaica Plain 30, Massachusetts

COSMETICS CONTAINING HORMONES

To the Editor: Your letter of July 6, 1945, asks what is the status of hormone-containing cosmetics so far as the Food and Drug Administration is concerned.

We have made some investigation of these products. There have been conflicting reports in the literature concerning the effects of estrogenic substances when applied locally. When applied in sufficiently large amounts there is no question but that they are absorbed and produce their usual systemic effects. When the amount of estrogens is reduced, however, to the quantity found in the products which are sold to laymen there seems to be no unanimity of opinion as to the physiologic effect. Some workers have reported the production of local edema apparently by imbibition of fluid into the collagen bundles without any systemic effect; others have claimed that it is not possible to produce a local result without at the same time causing a general one.

There has been a considerable amount of work on the carcinogenic properties of these materials. In highly susceptible strains of rats under very special conditions the administration of the estrogens has apparently produced carcinoma, but with ordinary laboratory animals and in all studies so far on human beings there is no evidence whatsoever that these products are carcinogenic.

We have investigated the files of a number of firms producing these products searching for evidence of injuries. We have not found such evidence.

To summarize, we have carefully reviewed the literature and consulted with many experts and, as a result of this, have arrived at the conclusion that at this time there is not sufficient legal evidence to show that the use of estrogens in the amounts found in products of this class is dangerous. We are skeptical of the benefits, if any, which accrue from the local use of these products but we do not believe that we are in a position to challenge qualified claims concerning them. We have consistently informed manufacturers that because of the uncertainty of the ultimate effect of the use of these products and because of their dubious value we do not look with favor on their distribution for lay use.

It was our plan to have conducted carefully controlled clinical studies to serve as the basis of appropriate legal actions if the products proved to be worthless, but preoccupation of the medical profession with more important studies during the war and the fact that our own medical staff has been made very much smaller has not made it possible to conduct these studies. We hope that they can be made soon after the termination of hostilities.

P. B. DUNBAR
Commissioner of Foods and Drugs

Food and Drug Administration
Federal Security Agency
Washington 25, D. C.

* * *

Although it is true that there is "no evidence whatsoever that these products are carcinogenic," the following statement (Nathanson, I. T. Endocrine aspects of cancer. *New Eng. J. Med.* **231**:764-770 and 795-802, 1944) deserves serious consideration.

> Strong evidence exists to indicate that endocrine factors are associated with some human tumors. There is as yet no conclusive proof that these influences are directly concerned with cancer, although an increasing number of cases are coming to light in which cancer developed after intensive estrogen therapy in organs such as the uterus and breast, which are normally stimulated by these hormones. It is probable that this is coincidence, but the association cannot be ignored. Present evidence suggests that the sex hormones are not in themselves carcinogenic. It is likelier that, as a result of excessive stimulation or atypical metabolism, the tissues of susceptible persons are conditioned to the action of a carcinogenic agent. — ED.

ANTIBIOTICS

To the Editor: The lack of good prefixes in Anglo-Saxon English has been one factor which has led to our pathetic and often laughable habit of making new words out of old Greek and Latin roots. The other factor is a natural instinct to hide our ignorance behind a false front of big words. Plain English words are always better than the jaw breakers that impressed our grandfathers.

Therefore a pox upon Dr. Wingo's "mycoantibiotics" and "chemoantibiotics" [a letter published in the July 19 issue of the *Journal*] and all other antibiotics. The silliness of the words is obvious when they are put into English: mold against life, drug against life and so on. Why not mold germ killer or drug germ killer, if we must have novelty!

I also prefer high blood pressure to hypertension, cure or care to therapeutics, tired nerves to neurasthenia, grog shop or gin mill to liquor saloon, printing to typography, headache to cephalalgia and thousands of other plain, clear short words to their repulsive four, five or six jointed Greek and Latin equivalents. I wish more people felt the same way.

ROBERT W. BUCK, M.D.
5 Bay State Road
Boston 15

(*Notices on page xiii*)

NOTICES

ANNOUNCEMENT

Dr. Theodore A. Potter announces the removal of his office from 99 Bay State Road to 372 Marlborough Street, Boston.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, AUGUST 16

FRIDAY, AUGUST 17

*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Parasitic diseases of the skin. Dr. E. A. Lafreniere. (Postgraduate clinic in dermatology and syphilology.) Amphitheater, Mallory Building. Boston City Hospital.

12:00 m.–1:00 p.m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, AUGUST 20

*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, AUGUST 21

*9:00–10:00 a.m. Medical clinic. Infants' Hospital.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, AUGUST 22

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

SEPTEMBER 13. The Hemorrhagic Diseases. Dr. William Dameshek. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.

OCTOBER 1–6. Medicolegal conference and seminar. Page 776, issue of June 28.

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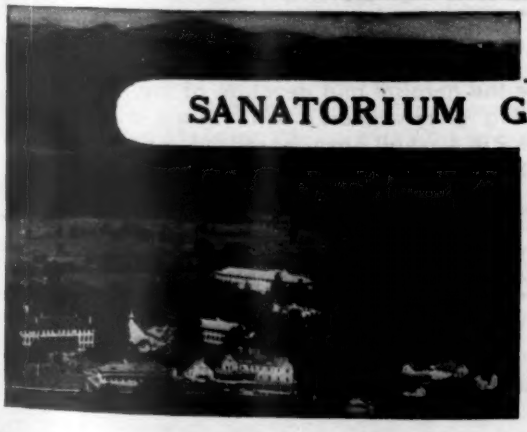

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1. **SUBJECT:** "Courage and Devotion Beyond the Call of Duty" — on the part of members of the medical profession — in military or civilian practice. Any contestant may portray either the military or civilian aspect of the subject (or both, if shown in one piece).

2. **MEDIA:** The physician-artist's choice of one of the following:

   1. PAINTING in oil or egg tempera.
   2. WATER COLOR, transparent or opaque.
   3. SCULPTURE in any medium.
   4. DRAWING in any medium.
   5. PRINTS, including etching, engraving, lithography, wood block and linoleum block (on paper or cloth).
   6. PHOTOGRAPHY, including bromoil, tinted and Kodachrome, as well as photo-montage.

   SUGGESTIONS: COMPLETE SKETCHES FOR MURAL DECORATIONS: In oil, egg tempera or water color drawing; PHOTO MURAL; BAS RELIEF SCULPTURE: are all eligible.

3. **ELIGIBILITY — See Footnote ★**

4. **DEFINITION — See Footnote ★**

5. **PRIZES: Forty-two prizes, divided amongst the two groups of physicians:**

To medical officers:	To civilian physicians:
1 $2,000 War Bond (E or F series)	1 $2,000 War Bond (E or F series)
10 $1,000 War Bonds (E or F series)	10 $1,000 War Bonds (E or F series)
10 $ 500 War Bonds (E or F series)	10 $ 500 War Bonds (E or F series)

No physician may submit more than one piece nor win more than one of the 42 prizes. No physician is eligible for a prize unless he also submits for exhibition at either the 1945 or the 1946 annual exhibition of the A.P.A.A. at least one other original work (not previously exhibited at an A.P.A.A. Exhibition) in any medium, on any subject of his own choice. Prizes will be awarded on a basis of conception and execution, irrespective of medium employed.

6. **JUDGES — See Footnote ★**

7. **EXPIRATION DATE — See Footnote ★**

8. **PURPOSE OF THE COMPETITION:** To memorialize the heroism and devotion of the medical profession in war and peace. All exhibitors (including prize-winners) shall retain ownership of their pieces. It is understood, however, that the A.P.A.A. shall have reproduction rights and also the privilege, for a period of three years after the close of the contest, of displaying prize-winning objects, at art museums, libraries, county medical societies, medical schools, hospitals, and similar institutions for the purpose of enhancing the public's estimate of the medical profession. The Association shall also have the right to offer institutions such as those mentioned above, the privilege of copying any of the prize-winning objects for use as murals, cornerstones, friezes, architectural designs, etc. — for the purpose of memorializing the medical profession's importance in war and in peace.

★ **FURTHER INFORMATION** available on request of the Association's Secretary, Dr. F. H. Redewill, Flood Bldg., San Francisco, Cal., or Mead Johnson & Co., Evansville 21, Ind., U.S.A.